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Developments in direct acoustic cochlear stimulation

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Voorwoord

Hoewel een PhD behalen voor velen een eindpunt is, betekent dit voor mij ook een opstap om verder onderzoek te blijven doen. Tegelijk is het goed om stil te staan bij de zovelen die me geholpen hebben dit project af te werken.

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Abstract

Hearing problems have been associated with poor quality of life, cognitive decline and a source of frustration. Over the past years, an essential progress has been made in hearing aids improving the wearing comfort, speech processing in noise and wireless connectivity. In a subgroup of patients with a combination of an important sensorineural hearing loss and a conductive component, defined as severe to profound mixed hearing loss, hearing rehabilitation was lagging behind. Conventional middle ear surgery and/or hearing aids would not suffice to overcome the degree of hearing loss and often local anatomical issues were complicating the hearing aid use. This subgroup is growing in number because of an increased awareness for hearing with two ears and for communicating. Also because of an aging population, the sensorineural hearing loss component is becoming increasingly important.

With the recent development of a new hearing system, a direct acoustic cochlear implant (DACI), the inner ear can be stimulated acoustically at the oval window. In this way, the amplified signal is provided directly to the cochlea and pathological external and middle ear structures are bypassed. This dissertation explores, for the first time, the functioning of direct acoustic cochlear stimulation in several domains. First, as guidance for evidence-based research, a systematic review of the literature on the hearing rehabilitation of mixed hearing loss was carried out. Next, the clinical application and thorough evaluation of DACI compared to the best current alternative are described. Finally, objective electrophysiological measures and new coupling strategies for DACI are developed.

In the first study, the clinical outcome and safety of a whole range of acoustic hearing implants in adults with mixed hearing loss was assessed through a systematic review of the literature. It was concluded that acoustic hearing implants and the respective various coupling strategies were beneficial in terms of speech perception in quiet, patient-reported outcome measures and safety

regarding residual hearing. Overall, the level of evidence and the quality of the included studies was judged to be moderate to low.

The second study consisted of a prospective, multicenter evaluation of nineteen subjects with severe to profound mixed hearing loss due to several etiologies. The DACI treatment was compared to the best-aided preoperative treatment. The mean speech reception threshold (SRT), a measure for speech in noise understanding and representative for real-life communication, improved with 7.9 dB compared to the preoperative aided condition for the study cohort. A mean postoperative aided SRT of 2.6 dB SNR was noted. Patient-reported questionnaires indicated a significant global benefit in hearing ability and in quality of life. The DACI surgery was regarded as a safe and efficient treatment.

In the third study, we focused on the development of an objective electrophysiological assessment of the device's coupling and stimulation of the entire auditory pathway. By investigating the feasibility of evoked auditory transient (ABR) and steady-state responses (ASSR), we opened the path for future intra-operative applications. Responses were recorded to click trains in the 40 Hz and 90 Hz range in three DACI subjects. A direct stimulation setup for reliable auditory response recording was developed in a first set of experiments. Next, by comparing amplitude growth function and phase delay in the same stimulus range, validity of the recorded responses was confirmed in DACI subjects. Electrophysiological stimulation thresholds could objectively be determined from the ABRs and ASSRs in all subjects and the relation with behavioral thresholds was made. Estimated latencies were in agreement with electrophysiological auditory pathway studies, with apparent latencies of about 40 and 25 ms for 40 and 90 Hz, respectively. For the first time, auditory evoked potentials could reliably be recorded and analyzed in patients with a digital speech processing DACI.

The fourth study aimed to explore the coupling of a DACI transducer to an anatomically easy accessible inner ear site, being the lateral semicircular canal (LC). This could simplify and shorten the surgical procedure. Fresh-frozen human cadaver heads were implanted with the DACI device stimulating the LC in different coupling situations. The LC was kept intact, blue-lined (i.e. thinning but keeping the last shell of bone closed) or opened, respectively, and each condition was compared with standard oval window coupling. As a measure of

the performance of the device and its coupling efficiency, the round window velocity was determined using a laser Doppler vibrometry setup. Pairwise comparisons in three frequency ranges showed that round window velocity was significantly lower in case of intact LC stimulation than in the standard oval window coupling condition, confirming the added value of direct inner ear stimulation. Equivalent output calculations showed a modest but significant added value of blue-lining over the intact condition. Opening the canal resulted in a significantly higher round window velocity than in the intact or blue-lined conditions for all frequency ranges, similar to the oval window coupling. Experimentally induced stapes footplate fixation did not impede the DACI performance when stimulating the opened LC.

In the different studies in this project important steps have been made towards reliable hearing rehabilitation, even in difficult listening situations, objective electrophysiological measures and easier surgery in the challenging treatment of severe to profound mixed hearing loss.

Korte Inhoud

Gemengd gehoorverlies ontstaat door de combinatie van geleidingsverlies, zoals bij buiten- en/of middenoorproblemen, met een binnenoorslechthorendheid. In de (zeer) ernstige vorm, kunnen hoortoestellen of middenoorchirurgie vaak onvoldoende versterking aanbieden. In de afgelopen decades werden verschillende akoestische hoorimplantaten ontwikkeld met gunstige functionele resultaten voor louter conductief of beperkt gemengd gehoorverlies. Helaas kon de groep van patiënten met (zeer) ernstig gemengd gehoorverlies niet of onvoldoende geholpen worden. Zeker niet in moeilijke luistersituaties, zoals in het dagelijkse leven vaak voorkomt. Hierdoor onstaan toenemende communicatie-problemen, sociale isolatie en soms zelfs cognitief verval. Daarenboven neemt dit patiëntenaandeel toe, mede door toenemende veroudering van de wereldpopulatie en het belang van horen met twee oren.

Recentelijk werd een nieuwe vorm van akoestische hoorimplantatie ontwikkeld. Via een prothese doorheen de stijgbeugelvoetplaat, ter hoogte van het ovale venster, wordt het binnenoor of cochlea direct aangedreven door een nieuw elektromagnetisch hoorimplantaat. Preliminaire studies met dit krachtig direct akoestisch cochleair implantaat (DACI) toonden een veelbelovende verbetering van het hoorvermogen aan in een selecte groep van patiënten. Een verdere implementatie in de kliniek werd echter nog niet uitgevoerd gezien vergelijkende klinische en experimentele studies, die het effect van deze stimulatie-vorm onderzochten, vooralsnog ontbraken. Dit doctoraatsonderzoek onderzocht, als eerste, verschillende aspecten van direct akoestisch cochleaire stimulatie zowel op het klinische vlak als op het electrofysiologisch en anatomisch experimenteel vlak.

Vanuit een “evidence-based” oogpunt werkend, werd als eerste doel van dit doctoraatsonderzoek de literatuur retrospectief en systematisch nagekeken om de huidige behandeling van puur gemengd gehoorverlies in kaart te brengen. Een bijzondere focus lag op veiligheid met betrekking tot het restgehoor,

spraakverstaan en subjectieve tevredenheid van de patiënt zelf. Hieruit bleek dat de meeste akoestische hoorimplantaten efficiënt zijn voor spraakverstaan in stilte, veilig zijn en dat de patiënt tevreden is. Kwaliteitsvolle vergelijkende studies rond spraakverstaan in achtergrondruis ontbraken echter, zeker voor de (zeer) ernstige vorm van gemengde slechthorendheid.

Vervolgens werd een prospectieve, multicentrische klinische studie uitgevoerd. De behandeling van direct akoestische cochleaire stimulatie werd onderzocht in vergelijking met het best mogelijke alternatief, zijnde een hoortoestel of een beengeleidingstoestel. De resultaten gaven een duidelijke verbetering in spraakverstaan met DACI aan, zowel in stilte als in ruis, met een gemiddelde verbetering van 7.9 dB ten opzichte van de preoperatieve spraakverstaanbaarheidsdrempel mét hoor- of beengeleidingstoestel. Vragenlijsten toonden een duidelijke verbetering in het hoorvermogen en de levenskwaliteit aan. De chirurgie werd veilig en efficiënt geacht.

De derde doelstelling in dit doctoraatsonderzoek was het ontwikkelen van elektrofysiologische methoden om via objectieve gehoormetingen de efficiëntie van direct akoestische cochleaire stimulatie na te gaan. In een eerste reeks van experimenten werden technische aspecten rond de codering van de DACI-spraakprocessor ontrafeld en een directe stimulatie-methode ontwikkeld voor het opmeten van auditief geëvokeerde potentialen, di een vorm van auditieve elektro-encefalogram opmeting. Vervolgens werd in dit onderzoek aangetoond, in DACI-dragers, dat zowel auditory brainstem responses (ABR) als auditory steady-state responses (ASSR) betrouwbaar opgemeten konden worden met deze stimulatie-methode op een niet-invasieve manier. Door het vergelijken van de groei in amplitude en fase van de antwoorden op verschillende klik-frequenties, konden de antwoorden gevalideerd worden. De opgemeten latentietijden kwam overeen met in de literatuur gerapporteerde latentietijden voor akoestische stimuli.

Als vierde doelstelling in dit doctoraatsproject werd ingezoomd op ontwikkelen van een eenvoudige koppelingsmethode voor DACI stimulatie van het binnenoor. Door het toestel rechtstreeks te koppelen op het lateraal semicirculair kanaal van het evenwichtsorgaan, kan men het openen van de faciale recessus vermijden. Zo worden risico's op facialisparese, net zoals bij cochleaire implantatie, vermeden. Vers diepgevroren, menselijke

kadaverhoofden werden geïmplanteerd waarbij de koppelingsmethode onderzocht werd ten opzichte van de standaard, ovale vensterkoppeling. Dit werd uitgevoerd door het opmeten van de trillingsnelheid van het ronde venster membraan met een laser Doppler vibrometer. Statistisch gepaarde vergelijkingen toonden aan dat met het openen van het lateraal kanaal een vergelijkbare versterking bekomen werd als met de standaard, ovale venster koppeling. Het lateraal kanaal intact laten of enkel uitdunnen, het zogenaamd 'blue-linen', gaf onvoldoende versterking. De koppeling aan het geopend lateraal kanaal, gaf voldoende breedspectrum versterking, zelfs in geval van een experimentele fixatie van de stijgbeugelvoetplaat, zoals bij otosclerose wordt gezien.

Samenvattend toonde dit doctoraatsonderzoek aan dat direct akoestische cochleaire stimulatie een veilige en efficiënte therapie is voor (zeer) ernstige gemengde slechthorendheid, zelfs in moeilijke luistersituaties. Er werd, voor de eerste maal, onthuld dat objectieve, electrofysiologische metingen uitvoerbaar zijn met dit digitaal akoestisch hoorimplantaat. Bovendien werd experimenteel aangetoond dat het binnenoor voldoende direct gestimuleerd kan worden via het geopend lateraal semicirculair kanaal. Deze resultaten kunnen tot een herziening van de huidige therapie van (zeer) ernstig gemengde slechthorendheid leiden.

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Acronyms and abbreviations

ABR	Auditory Brainstem Response
AC	Air Conduction
AEP	Auditory Evoked Potential
AHI	Acoustic hearing implant
AMEI	Active Middle Ear Implant
AMLR	Auditory Middle Latency Responses
APHAB	Abbreviated Profile of Hearing Aid Benefit
ASSR	Auditory Steady-State Response
BAHA	Bone-Anchored Hearing Aid
BC	Bone Conduction
BCI	Bone Conduction Implant
CI	Cochlear Implant
DACI	Direct Acoustic Cochlear Implant
dB HL	Decibel Hearing Level
dB SPL	Decibel Sound Pressure Level
dBpeFS	dB peak equivalent Full Scale
df	degree of freedom
ECoG	Electrocochleography
EEG	ElectroEncephaloGram
e.g.	exempli gratia: for example
eq	Equivalent
FMT	Floating Mass Transducer
IIB	Implant-In-a-Box
i.e.	id est: that is
IR	Interquartile Range
HA	Hearing Aid
HDSS	Hearing Device Satisfaction Scale
HUI	Health Utilities Index
H_{EV}	Electrovibrational Transfer Function
H_{TV}	Middle Ear Transfer Function
Hz	Hertz
LC	Lateral semicircular Canal
LDV	Laser Doppler Vibrometry
L34	L34 research speech processor
L_E	Equivalent Sound Pressure Level

$L_{E,max}$	Maximum Equivalent Sound Pressure Level
MET	Middle Ear Transducer
MHL	Mixed Hearing Loss
MRI	Magnetic Resonance Imaging
POD	POD programming device
PORP	Partial Ossicular Replacement Prosthesis
PROM	Patient-Reported Outcome Measures
PTA	Pure Tone Average
r	Effect Size
RBA	Software platform for the Recording and analysis of Brain responses to Auditory stimulation
RF	Radio Frequency
RME	RME Hammerfall DSP Multiface sound card
RMS	Root Mean Square
RW	Round Window
RWM	Round Window Membrane
SAL	Sensorineural Acuity Level test
SD	Standard Deviation
SNHL	Sensorineural hearing loss
SNR	Signal-to-Noise Ratio
SRT	Speech Reception Threshold
TORP	Total Ossicular Replacement Prosthesis
V	Volt
VSB	Vibrant Soundbridge
W	Watt

Chapter 1
General introduction

1.1 Motivation for the present research

In humans, problems with hearing and communication are regarded as highly frustrating and associated with a poor quality of life, certainly among older people (Chia et al, 2007). Sustained hearing loss can result in a decrease of general health and mood disorders, such as depression (Gopinath et al, 2009). Prospective studies have shown that hearing loss is independently associated with the all-cause dementia (Lin et al, 2011a). In addition to middle ear surgery, hearing aids (HAs) are the primary treatment option in the management of hearing rehabilitation but reports state that up to 24% of the HA owners never wear them (Hartley et al, 2010). The main reasons for non-use were identified as an insufficient benefit provided by the HA and the comfort related to wearing the HA (McCormack & Fortnum, 2013). The first issue is more frequently encountered in case of a substantial degree of hearing loss, the latter in case of anatomical problems related to external or middle ear problems.

In addition to acquired middle ear pathologies, many patients are presenting a sensorineural hearing loss demanding adequate amplification. The number of patients keeps growing because of an aging population. Furthermore, a slowly raising awareness for hearing handicap as well as the progress in technology has driven more individuals to seek help. New implantable hearing systems have been developed in the past decades. Cochlear implants (CIs) have proven themselves very effective for severe to profound sensorineural hearing loss, even when associated with chronic otitis media (Leung & Briggs, 2007) or far advanced otosclerosis (Merkus et al, 2011). They provide electrical cochlear stimulation and are regarded as a well-established therapy. CI treatment, however, is associated with mostly an important rehabilitation period. Present-

day technology does not adequately code speech's fine structure and shows limited F_0 information transmission (Toung et al, 2004; Zeng et al, 2008; Milczynski et al, 2009; Blamey et al, 2013). Consequently, many experts advocate that when some cochlear remaining function exists, it should be exploited with a reliable alternative treatment, embedded in a powerful acoustic hearing implant (AHI) coupled directly to the inner ear. The clinical implementation of this acoustical stimulation and its potential benefits needs to be investigated prospectively.

The attachment of such an AHI to the middle or inner ear structures is defined as the 'coupling'. Currently, as so often in middle ear surgery, this coupling mainly relies on the skills, experience and visual inspection of the surgeon during surgery. Hearing results can only be appreciated after a period of postoperative healing. Although tools have been developed to provide surgical feedback on the coupling (Jenkins et al, 2007; Karkas et al, 2012), the underlying aided auditory pathway has not been evaluated. Just as cochlear implantation is partially relying on intra-operative auditory nerve feedback; electrophysiological methods need to be developed for the objective evaluation of the coupling of AHIs to the inner ear. So far, absolute electrophysiological thresholds have not been determined with AHIs. Accordingly, with the perspective of an increasing patient population with severe to profound mixed hearing loss (MHL), due to aging, and new evolutions in electro-acoustic hearing systems, objective electro-physiological measures for a recently introduced hearing implant, a direct acoustic cochlear implant (DACI), are developed and analyzed in this PhD project. Furthermore, a new surgical technique for DACI coupling to the inner ear is evaluated, potentially broadening its indication range and simplifying the surgical implantation.

In this chapter, a general introduction on hearing loss (1.2) and its treatment with acoustic hearing implants (1.3) are given. Moreover, methods for the objective evaluation of a hearing implant's functioning (1.4) and the patient's audiological and self-reported evaluation (1.5) are provided. The introduction is followed by the objective and an outline of the PhD project.

1.2 Hearing loss

Hearing loss is a highly prevalent impairment amongst society, with an enormous impact on a person's quality of life. In 2012, the World Health Organization released new estimates on the magnitude of disabling hearing loss, defined as a hearing loss greater than 40 dB HL in the better hearing ear in adults and a hearing loss greater than 30 dB HL in the better hearing ear in children. Over 5% of the world's population – 360 million people – has disabling hearing loss (328 million adults and 32 million children). The prevalence increases with age, and more than one third of people older than 65 years have clinically significant hearing loss. The prevalence in this age group is the greatest in Asia Pacific, South Asia and sub-Saharan Africa. It is expected to be between 18 - 50% from 2010 - 2020 in all regions.

Different degrees of hearing loss are described using pure-tone thresholds at 0.5, 1, 2 and 3 or 4 kHz of audiograms. The following categories are distinguished: mild HL (25 – 40 dB HL), moderate (40 – 55 dB HL), moderate-severe (55 – 70 dB HL), severe (70 – 90 dB HL) and profound (> 90 dB HL). In this project we will mainly deal with subjects with severe to profound hearing loss.

For clinical and audiological diagnosis and therapy it is important to associate the hearing problem with its origin. Principally, three kinds of peripheral hearing disorders are differentiated, i.e. conductive, or sensorineural or their combination named mixed hearing loss. In the next sections, first the hearing loss and the etiology will be discussed, next the possible therapy will be elaborated. Accordingly, recent insights in the pathophysiology of hearing loss, relevant for this project, based on up-to-date reviews about cochlear physiology and neurobiology (Guinan et al, 2012; Knipper et al, 2013), are discussed briefly throughout the following sections.

1.2.1 Conductive hearing loss

Conductive hearing loss occurs due to a conflict with the mechanical reception or amplification of sound to the cochlea. The interference is in the external or middle ear involving the ear canal, tympanic membrane or middle ear ossicles. In humans, an ossicular chain spans the middle ear cavity linking the tympanic membrane to the inner ear. An important etiology of persistent conductive

hearing loss is otosclerosis, a condition characterized by lesions in the endochondral bone of the otic capsule, causing progressive fixation of the stapes footplate in the oval niche of the cochlea (Chole & McKenna, 2001). In its active phase, known as otospongiosis, highly vascular lesions resorb bone surrounding the inner ear. The active lesions mature into calcified otosclerotic plaques that are responsible for stapes fixation. Other causes of conductive hearing loss can be enumerated: tympanic membrane perforation; chronic otitis media with cholesteatoma and/or retraction pockets compromising the ossicular chain's integrity; tympanosclerosis, explained as a scarring process in the middle ear; congenital or acquired malformation of the external and/or middle ear; temporal bone fracture.

1.2.2 Sensorineural hearing loss

Sensorineural hearing loss, the most common type of hearing loss among adults, results from damage to or malformation of the cochlea and the sensorineural elements that lie internally beyond the oval and round windows. These elements include the auditory nerve and its connections in the brainstem. The most common cause of sensorineural hearing loss is age-related hearing loss or presbyacusis. This gradual bilateral hearing loss, associated with aging, is due to a progressive degeneration of cochlear structures, auditory nerve and more central auditory pathways. The functional integrity of three major components of the cochlea, organ of Corti, stria vascularis / spiral ligament, and spiral ganglion neurons are compromised (Kim et al, 2014). Recently, cellular oxidative stress and inflammatory responses have been reported to facilitate morphological and ultrastructural degeneration (Massudi et al, 2012). The hearing loss usually begins with the high frequencies then progresses to sounds of middle and low frequencies. If mainly outer hair cells are affected, supra-threshold stimuli will still evoke synchronized neural potentials in the auditory nerve and brainstem pathways. Therefore, affected subjects typically benefit from hearing aids or acoustic hearing implants. In case of inner hair cell synapse or auditory nerve defects, as in auditory neuropathy, even with audibility being normal or restored, speech comprehension is impaired and often not improved with hearing aids (Moser et al, 2013).

Another frequent cause is sound induced hearing loss. This is generally associated with a reduction in cochlear sensitivity due to outer and inner hair cell loss (Liberman & Dodds, 1984). Recent animal investigations, likely to apply for humans as well, show that excitotoxic effects of noise at afferent synapses, causing a loss of afferent fibers, are also to be taken into account (Lin et al, 2011b). Secondary to a degeneration of the afferent dendrites of auditory fibers, a neurodegeneration at the level of the spiral ganglion neurons can occur (Knipper et al, 2013). Experiments on noise-induced hearing loss in chinchillas (Henry & Heinz, 2012) showed that neural coding of signals is less resilient to background noise than normal. This confirms the need for new technologies to improve the signal-to-noise ratios for subjects with sensorineural hearing loss. Other causes of sensorineural hearing loss are known as ototoxic hearing loss; Morbus Menière; congenital causes, such as a connexine 26 mutation, or perinatal causes, such as rubella infection. A 'cochlear' otosclerosis is associated with sensorineural hearing loss. It has been estimated that 1.6% of patients with otosclerosis will eventually develop profound hearing loss (Shea et al, 1999).

1.2.3 Mixed hearing loss

Mixed hearing loss is defined as a combination of sensorineural hearing loss, due to (peri-)cochlear dysfunction, superimposed with a conductive component, caused by middle ear pathology. As mentioned above, certainly the advanced form of otosclerosis is frequently associated with MHL. Also labyrinthine complications of previous stapes surgery can be associated with severe to profound MHL. A second pathology possibly resulting in MHL is chronic otitis media. Due to inflammation associated with for instance tympanic membrane retraction, cholesteatoma or previous surgery, both conductive as sensorineural hearing loss can occur (Chapter 2). Poor hearing outcome, even after proper placement of a total or partial ossicular replacement prostheses (TORP or PORP) (Linder et al, 2009), has been explained by diminished or absent ventilation of the middle ear space, prosthesis extrusion, tympanosclerosis, scar tissue, tympanic membrane lateralization and eroded ossicles. Morphological abnormalities like congenital malformations could present themselves with MHL, although isolated conductive hearing loss is more frequently associated. Congenital aural atresia consists of a dysplastic or absent external ear and a

varying degree of middle and inner ear malformations with possible aberrant facial nerve anatomy. The incidence of aural atresia is about 1:10.000 births (Melnick et al, 1979). Other more seldom causes are associated with trauma: labyrinthine contusion or temporal bone fracture with stapes footplate fracture.

Severe to profound MHL remains a challenge for adequate hearing rehabilitation. If conventional HAs or middle ear surgery fail, a treatment gap exists between two indication ranges: most AHIs (see section 1.3) are used effectively in conductive hearing loss or moderate MHL (Luers et al, 2013), CIs are reserved for severe to profound *sensorineural* hearing loss. Recently, a new type of hearing system has been developed filling up this gap, a direct acoustic cochlear implant (DACI). In profound MHL, combining conductive with sensorineural hearing loss, thus also neuronal degeneration of both efferent and afferent fibers, DACI technology faces similar challenges as hearing aids.

1.3 Acoustic hearing implants

Over the last decades hearing aids could not always overcome certain anatomical and audiological challenges, in spite of a constant improvement. Examples of anatomical issues are severe chronic otitis externa and congenital aural atresia (Verhaert et al, 2011). Also in chronic otitis media with sequelae at the tympanic membrane (perforations or tympanosclerosis) or large open (radical) cavities, the use of conventional HAs is problematic and unsatisfactory. Audiological issues include feedback issues, sound quality or bothersome occlusion effect.

Although initially proposed for sensorineural hearing loss (Truy et al, 2008; Verhaegen et al, 2008), most AHIs are currently used for conductive or mixed hearing loss. They can be divided in active and passive implants, whether the function of the implants depends on external energy or not. Currently, these AHIs cover the broad range of a mostly passive bone conduction system, such as bone-conduction implants (BCI), to an active middle ear implant (AMEI) and DACI. Figure 1.1 provides an overview of different implant types and depicts their respective coupling site in the ear.

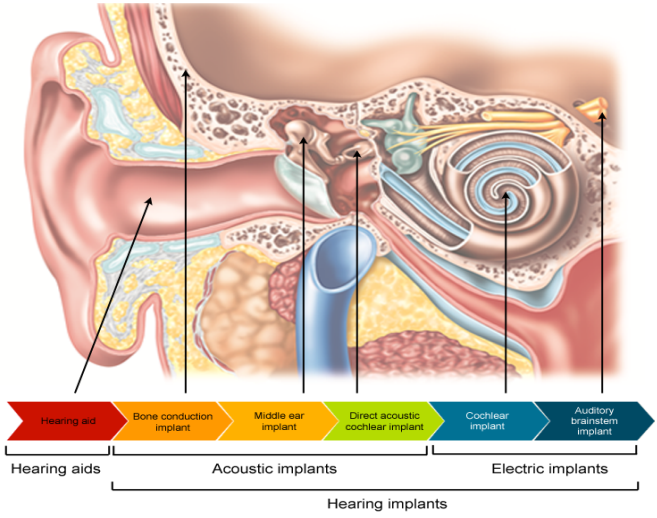

Figure 1.1 Comprehensive overview of hearing implants and their respective coupling site (Delaere (2007), illustration adapted for hearing implants overview).

Different amplification options for MHL were compared in a recent clinical study of Zwartenkot et al (2014), determining the maximum output of these devices in dB HL. A short description of the most frequently used devices is given below, because of its relevance for Chapter 2 and 3. HAs and CIs were not described separately, as they are regarded as well-known therapies. In Chapter 2 a systematic review with clinical outcomes is described more in detail for the different systems.

1.3.1 Active middle ear implant

Active middle ear implants couple to a middle ear structure. Semi-implantable AMEIs consist of an implanted part with a mostly electromagnetic driver and an externally worn speech processor, similar to a CI. In 1996 Fisch implanted the Symphonix device, later named Vibrant Soundbridge, with its floating mass transducer or FMT (MED-EL, Innsbrück, Austria), and coupled it to an intact ossicular chain at the level of the long process of the incus (Goode, 1995; Lenarz et al, 1998; Fisch et al, 2001) (Figure 1.2).

Another AMEI is the Otologics device, with its middle ear transducer or MET (Otologics & Cochlear™, Boulder, CO, USA), involving the semi-implantable MET® system and the fully implantable Carina® system. In the totally implantable

system, the microphone and audio-processor package, including its battery, is placed under the skin.

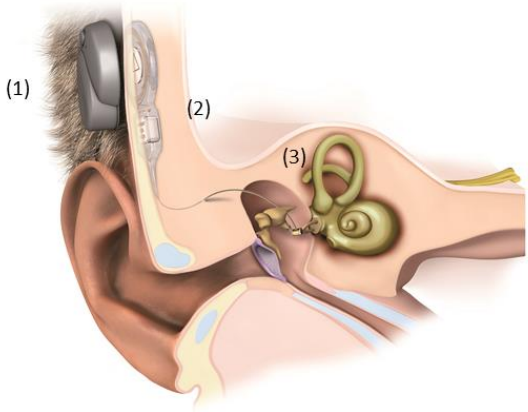

Figure 1.2 Schematic presentation of a Vibrant Soundbridge, consisting of (1) speech processor, (2) implant and (3) FMT coupled here to the incus. (MED-EL)

Later on, broadening the indication to conductive and mixed hearing loss because of ossicular chain's deformities or absent ossicles, new coupling sites were investigated. Colletti et al (2006) were the first to report the round window (RW) coupling for Vibrant Soundbridge. Subsequently, many reports on different types of couplers (e.g. fascia, cartilage and titanium couplers) at the remaining stapes, oval or round window structures followed rapidly, each with its own advantages and disadvantages (Baumgartner et al, 2010; Luers et al, 2013; Schwab et al, 2012; Tringali et al, 2010; Verhaert et al, 2011). With the introduction of titanium couplers (Luers et al, 2013), it is expected that variability in functional outcome will decrease, but dislocation of a non-fixed stimulator (e.g. Vibrant Soundbridge at the round window) with loss of amplification remains a possibility (Bernardeschi et al, 2011). In selected cases of chronic otitis media with open (radical) cavities, a two-staged intervention with first closure of the middle ear cleft, abdominal fat obliteration and six months later AMEI implantation is advised (Verhaert et al, 2013b). This helps to avoid cholesteatoma recurrence and possible foreign body infection with a risk of extrusion. A more detailed overview of AMEIs can be found in Chapter 2 and in Tysome et al (2010).

1.3.2 Bone conduction implant

Bone conduction results from two modes of vibration of the human skull: the inertial mode, in which the skull vibrates as a unit and the compressional mode, in which the skull is divided into a number of compartments (Tonndorf, 1966). Acceleration of the temporal bone surrounding the inner ear causes inertial displacements of uncompressible cochlear fluids and subsequently vibrations of the basilar membrane (Stenfelt & Goode, 2005). Bone conduction implants, per- or transcutaneous, osseointegrated or not, mainly couple to the temporal bone and use the bone conduction pathway. The most widely-used type, a BAHA (Bone-Anchored Hearing Aid), with different processors from Cochlear Ltd. or Oticon Medical, can overcome the sensorineural hearing loss component up 45 to 50 dB HL, as shown with the body-worn Baha Cordelle (Zwartenkot et al, 2014). Nevertheless, the life-long daily care and the risk of skin infection with the skin-penetrating abutment have driven the development of transcutaneous devices (Snik et al, 2005). Considerably less powerful, transcutaneous BCI preserve the skin's integrity. Commercially available transcutaneous applications are the recent BAHA Attract system from Cochlear, the Otomag Alpha 1 device (Sophono, Boulder, CO, USA) and the active BCI from MED-EL, named Bonebridge. Probably in the near future, more active BCI systems will become available. Extensive research work on BCIs has been done before and lies beyond the scope of this thesis.

For severe to profound MHL, only powerful implants can produce sufficient output to stimulate the remaining cochlear reserve, indicating the need for direct acoustic cochlear stimulation, as shown in Figure 1.3 (Zwartenkot et al, 2014).

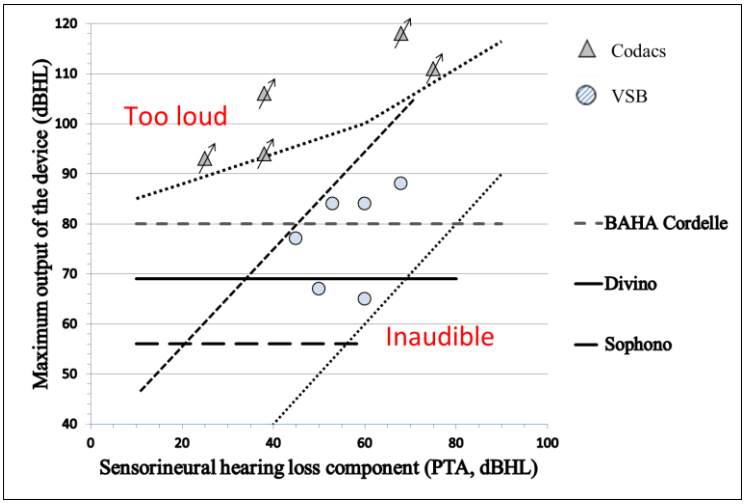

Figure 1.3 Maximum output of various hearing devices in relation to the sensorineural hearing loss component. For BCIs the maximum output is presented as horizontal lines. For the Vibrant Soundbridge (VSB) and DACI (Codacs) devices the maximum output values are presented as individual data points (Zwartenkot et al, 2014).

1.3.3 Direct acoustic cochlear implant

Direct acoustic cochlear implants drive directly the inner ear's perilymph with acoustical stimulation. Former reports of coupling an AMEI to a fixed stapes or to the RW in case of stapes fixation, showed limited benefit (Devèze et al, 2010; Verhaert et al, 2011). To this end, in case of severe to profound MHL because of stapes footplate fixation, as in advanced otosclerosis, direct acoustic stimulation was explored. Häusler et al (2008) described the coupling of a DACI[1] actuator to the cochlea's vestibule through a stapes prosthesis in 4 patients after complete removal of the stapes footplate or stapedectomy. The study showed a clear benefit of direct acoustic cochlear stimulation compared to the preoperative situation and compared to a stapedectomy combined with a conventional hearing aid. This novel acoustic hearing implant was first designed and tested under the collaboration of the Ear, Nose & Throat department (Inselhospital, Bern), the hearing industry (Phonak AG), the cochlear implant industry (Cochlear Ltd) and microtechnology, with Häusler and Stieger being the

[1] Initial reports refer to DACI as DACS and both terms are used in the current literature.

main protagonists (Bernhard et al, 2006; Häusler et al, 2008). Also described as DACI, but less powerful, Schwab et al (2012) proposed the coupling of a Vibrant Soundbridge to a titanium prosthesis into the vestibule in three patients.
The current Codacs DACI system from Cochlear Ltd. (Sydney, Australia) consists of an external digital speech processor and an internal implant connected by a wireless radio-frequency (RF) transmission link that provides both power and a bidirectional communication link (Figure 1.4).

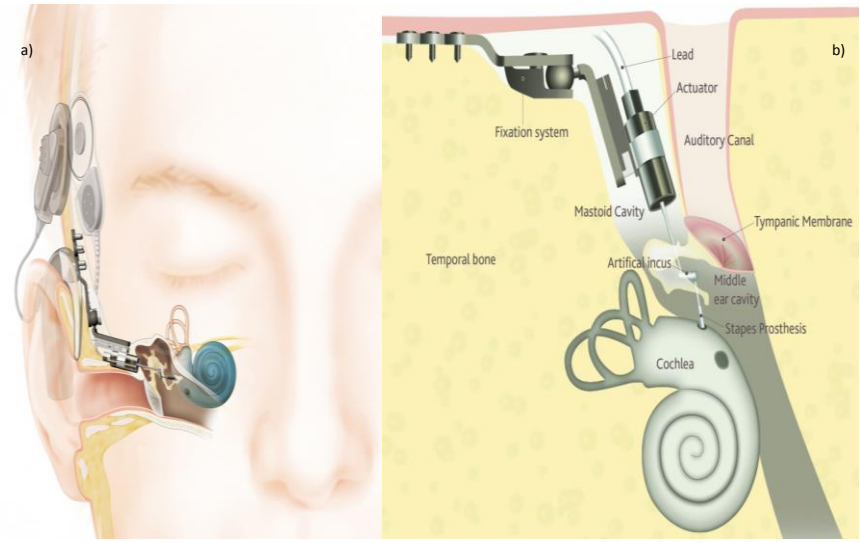

Figure 1.4 Codacs DACI system **a**) overview with speech processor and implant **b**) anatomical position. (Cochlear Ltd.)

The RF frames are decoded digitally in the implant and used to drive an electro-magnetic transducer in the middle ear (Bernhard et al, 2011). This transducer is fixed in the mastoid cavity with a fixation system, avoiding dislocation. Dislocation in case of direct inner stimulation could not only lead to a loss of amplification, but in worst case, to additional inner ear damage due to protrusion into the inner ear.

The electrical input signal is converted into a movement of an actuator, i.e. the artificial incus, in turn connected to a conventional stapes prosthesis at the level of the oval window. Opening the inner ear through a hole in the stapes footplate is known as a classic stapedotomy (as shown in Figure 1.5), but instead of coupling to the incus, the prosthesis is coupled to an artificial incus.

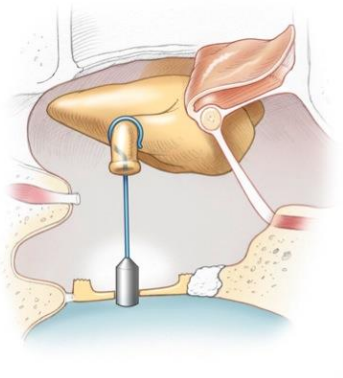

Figure 1.5 Classic stapedotomy with a stapes prosthesis coupled from the incus to the cochlea's vestibule, through a calibrated hole in the stapes footplate, in case of otosclerosis. Sagittal view of the oval window niche (Jackler, 2013).

The frequency response of the actuator was designed to mimic the middle ear transfer function (Bernhard et al, 2011). From intra-operative measurements, after coupling to the inner ear and healing, a smooth frequency response with broad spectrum amplification was noticed. With a frequency range of 100 to 10000 Hz and an equivalent maximal sound pressure output of over 125 dB SPL with a 1 mW power supply, the authors concluded that the device was well suited to treat severe to profound MHL (Häusler et al, 2008; Bernhard et al, 2011). The device has received CE approval for adult use in 2013.

As described in Chapter 3, the speech processor is usually fitted eight weeks postoperatively by the dedicated audiologist. An input transfer function, obtained during intra-operative measurements from the actuator with laser Doppler vibrometry (see section 1.4.3), is introduced in the user's fitting map. Sixty-three bins are combined into 20 frequency channels. In a stepwise manner, the wearer's threshold and uncomfortable level are measured with the implant. Next, prescription rules and procedures known from hearing aid fitting are used. These procedures are based on the desired sensation level or the most comfortable loudness level and are used to calculate the target parameters such as the maximum power output value and the gain. In several sessions, the speech processor can be adjusted according to the subjects' hearing loss and comfort. Different to electrical stimulation with CI, rehabilitation with acoustical stimulation is expected to be more rapid.

1.4 Objective measures for hearing implants

Evaluation of a hearing implant's functioning and its adjustment to the needs of the individual patient, the fitting, can be performed not only with subjective feedback but also, more independently, with objective instruments. Methods have been developed overcoming a certain degree of variability related to the voluntary and conscious reaction of the tested subject and the testing professional. Furthermore, these methods allow standardization of the implant's functional assessment and its concomitant scientific reporting.

During auditory stimulation, typical changes related to time-locked variations in an acoustical stimulus can be seen in an electroencephalogram (EEG). Geisler (1960) described averaging procedures to measure responses to clicks from the human scalp. These changes in the EEG, often seen as neuronal aggregates, are named auditory evoked potentials (AEPs). In response to acoustic stimuli, different parts of the auditory pathway are measured objectively and passively, this means without requiring response from the subject. Electric stimuli are rather used in combination with a CI electrode or for preoperative testing in CI candidates (Brown et al, 1990). AEPs may be classified as transient or steady-state responses to a short or continuous auditory stimulus, respectively. In the following section, first a selected overview of AEPs generated by acoustic stimuli, relevant for the research conducted during this PhD project, is given. A thorough and updated review on AEPs can be found in Picton (2013) and in Rance (2008). Next, a tool for objective quantification of hearing implant's performance in humans is described.

1.4.1 Transient responses

Generally spoken, transient responses occur with abrupt increases in stimulus' amplitude. Figure 1.6 provides a visual overview of different AEPs, divided according to their latency in relation to the stimulus. Electrocochleography (ECoG) responses arise directly from the cochlea and the auditory nerve and occur within the first 2 to 3 ms after an abrupt stimulus. The response typically consists of three components: the cochlear microphonic, the summation potential and the compound action potential. The compound action potential can also be described as N1. ECoG, most reliably obtained with invasive needle recording at the promontory near the round window, is clinically used for

hydrops labyrinthi measurements in Morbus Menière and auditory nerve monitoring for CI candidates or vestibular schwannoma surgery (Schoonhoven et al, 1995). Some authors use ECoG for comparative measurements during AMEI coupling at the RW (Colletti et al, 2012).

Far field recordings of the electrical activity in the auditory pathway up to the cortex can be obtained in the EEG measurement. Auditory brainstem responses (ABRs) are commonly defined as transient responses to broadband clicks or tone bursts and evaluated in the time domain. Together with ECoG, ABRs are regarded as short latency AEPs, i.e. before 10 ms after stimulus onset. Discovered more than 40 years ago (Jewett & Williston, 1971), the response is characterized as a wave labeled with different peaks related to several parts of the auditory pathway up to the level of the brainstem (Figure 1.6).

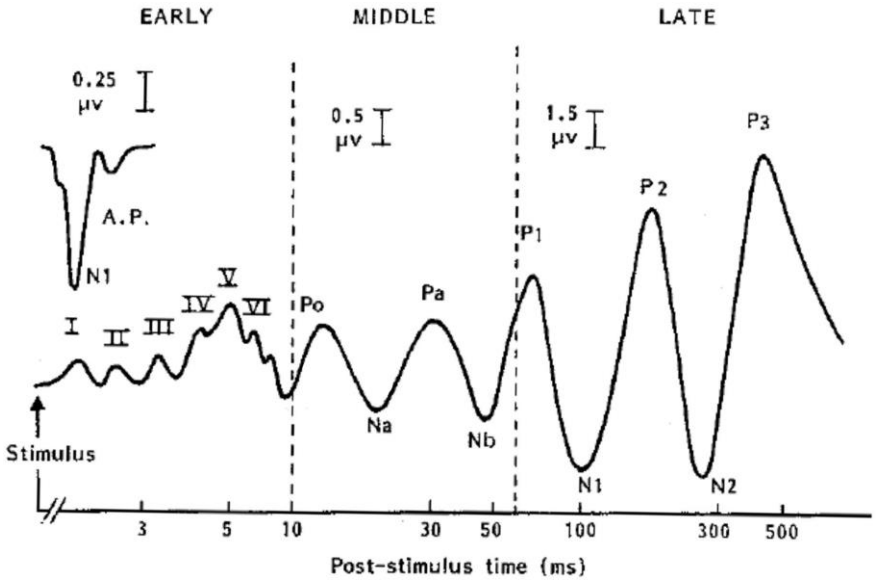

Figure 1.6 Auditory evoked potentials (McCormick, 2004).

Amongst others, Møller et al (1995) have partially identified the neuronal generators: peak I and II originate from the auditory nerve, peak III from the cochlear nucleus, peak IV from the superior olivary complex and peak V from the lateral lemniscus and inferior colliculus. Peak V is regarded as the most robust and ABRs are not affected by sleep or most anesthetics. Therefore the

click-evoked ABR has enjoyed wide-scale clinical use for auditory threshold determination, auditory neuropathy and detecting retrocochlear pathologies such as a schwannoma of the vestibular nerve (Debruyne, 1981; Hall, 2006; Koors et al, 2013). ABR threshold determination, regarded as the lowest stimulus level at which peak V is present, contains some drawbacks. The broadband click stimulus excites a large range of the basilar membrane, mainly around 1 to 3 kHz, but lacks frequency specificity. Visual inspection of the waveforms by the clinician is a more subjective element. Finally, the ABR does not contain information about the thalamocortical level of the auditory system. The use of tone bursts, chirps and complex stimuli is more and more exploited (Stapells & Oates, 1997; Skoe & Kraus, 2010). ABR methods using more narrow-band stimuli, such as these tone bursts, provide better correlation with behavioral hearing thresholds at different frequencies, but are considerably more time-consuming, (Gorga et al, 2006). In the past decade, chirp stimuli have been optimized to evoke larger response amplitude (Dau et al, 2000), compensating for temporal dispersion of the frequency components of a click stimuli at the basilar membrane. Recently, chirp stimuli have been created and implemented for the clinical recording of ABR showing a shorter detection time and a higher signal-to-noise ratio than the click (Elberling et al, 2007).

Auditory middle-latency responses (AMLRs) are defined as AEP with latencies between 12 and 50 ms after stimulus onset, using click or tone burst stimulation. AMLRs are recorded for the evaluation of the functional integrity of the auditory system beyond the level of the brainstem, for example in case of an auditory brainstem implant placement (Hall, 2006).

Long latency responses, also known as cortical evoked potentials, occur at latencies beyond 75 ms after stimulus onset. They are largely derived from the cortex. Frequency-specific evoked response thresholds are feasible, but their use is mainly limited to awake and cooperative subjects. Long latency responses are used to assess the integrity of the cortical auditory system, to diagnose auditory processing disorders and to assess speech perception skills (Hall, 2006).

1.4.2 Auditory steady-state responses

Auditory steady-state responses (ASSRs) are following responses from the brain or brainstem evoked by periodic stimuli or stimuli presented at a sufficiently high rate to cause an overlapping of the responses to successive stimuli (Stapells et al, 1984; Picton, 2013). They are generally assessed in the frequency domain and can typically be evoked by a sinusoidal amplitude- or frequency-modulated tone (Picton et al, 2003) or modulated white noise (Purcell et al, 2004). They can also be elicited by repeated clicks (Galambos et al, 1981) or tone bursts (Stapells et al, 1984). The largest response amplitudes are seen with stimuli around 40 Hz, but responses can also be recorded for other modulation frequencies, like around 20 and 80 Hz range (Cohen et al, 1991). As described in the upcoming section, the frequency specificity of the stimulus characterizes the ASSR response, making it advantageous for objective response audiometry. The response detection is completely objective as it is based on statistics. ASSRs are used for hearing threshold determination in infants (Luts et al, 2006; Alaerts et al, 2010) as well as in adults (Luts & Wouters, 2005) or for the monitoring of the remaining low-frequency hearing in case of electro-acoustic cochlear implantation (Haumann et al, 2012, unpublished data).

Response detection

A comprehensive overview on how ASSRs are obtained is shown in Figure 1.7, adapted from Rance (2008). In the following paragraph, different aspects of the ASSR recording and analysis are explained using the figure. The EEG signal can be recorded with surface electrodes as a small voltage signal, often expressed in microvolts (µV). Different scalp electrode positions have been suggested, although common placements for single channel ASSR recordings (Johnson & Brown, 2005) include the vertex (Cz) for the active (positive) electrode, ipsilateral mastoid (TP_9 or TP_{10}) for the reference (negative) electrode and the contralateral mastoid (TP_9 or TP_{10}) for the ground electrode, in accordance with the international 10-20 system (Malmivuo & Plonsey, 1995) (see Chapter 4 for the stimulation and recording paradigm applied in this PhD project). After the recorded EEG signal is amplified and filtered, it is divided into epochs with a fixed length, containing an integer number of stimuli responses. This allows for the representation of the EEG signal in the time domain, as shown in Figure 1.7. Epochs with recording artifacts such as muscle movements and skin potentials

are rejected to prevent the erroneous detection of neural responses and the distortion of response properties. As the recording continues and more epochs are collected into the data structure, they can be combined to sweeps (see 'Data structure' in Figure 1.7). The recorded sweeps contain both brain activity related to the stimulus, i.e. signal, in this case the ASSR, and activity that is not related to the processing of the stimulus, i.e. noise. Ergo, it is important to assess the signal-to-noise ratio (SNR) of the ASSR, i.e. the ratio of the signal power to the noise power defined in dB. Averaging, performed by adding sweeps together during the same ASSR recording to obtain an average sweep, results in a reduced spontaneous EEG activity in a recording that is not linked to the stimulus.

Stimulus parameters

ASSR stimuli are characterized by a carrier signal and a rate (see upper left panel in Figure 1.7). In this figure, a multiple-stimulus was used. The main advantage of the multiple-stimulus technique is the reduction in measurement time (Lins et al, 1996). A carrier signal varies in amplitude or frequency at a certain rate. The rate of the stimulus is defined as the stimulus repetition frequency in case of click or tone burst stimuli, or the modulation frequency in case of modulated stimuli. The rate of the stimulus is a crucial aspect because it is the exact frequency at which the response is evaluated in the EEG spectrum. Furthermore, the modulation rate determines where in the auditory pathway the corresponding ASSR is generated. And so the ASSR, characterized by its amplitude and phase, can be derived from the bin corresponding to the frequency spectrum of the average epoch. As shown in Figure 1.7 bottom row, steady-state responses can be plotted in different ways. Besides the amplitude or power spectrum, a polar notation is commonly used. A polar plot represents the response as a vector, with the amplitude of the response in the length of the line and the phase being the angle measured counter-clockwise from the x-axis (Picton et al, 2003).

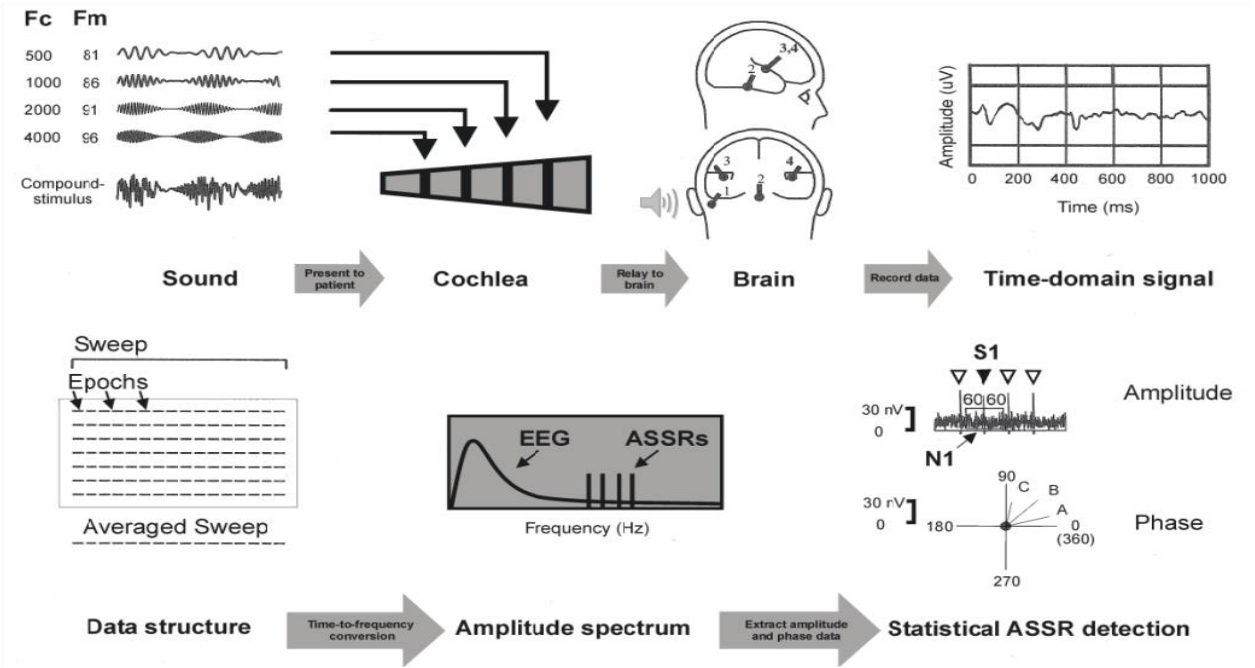

Figure 1.7 Overview of ASSR testing. Fc = carrier frequency; Fm= modulation frequency (Rance 2008).

Different approaches have been described to assess whether a response is significantly different from noise (Picton et al 2003). A commonly used method involves an *F*-test in the time or spectral domain (as shown in the upper panel of Figure 1.7), calculating the *F* ratio of the power of the response in the signal frequency bins relative to the mean power of n adjacent frequency bins (Lins et al, 1996). In the complex domain, a one-sample Hotelling T^2 test can be used to compare the average real and imaginary parts, plotted on the x- and y-axis, respectively, of the response bin against the variability of the same response bin across epochs (Hotelling, 1931; Hofmann & Wouters, 2012). Both methods have the same degrees of freedom and power, they can be applied conversely (Dobie & Wilson, 1996). Additionally, a two-sample Hotelling T^2 test can be used to compare the response bins for two measurements using adjacent stimulation rate to determine the presence of a neural response (Hofmann & Wouters, 2012).

An important notice for clinical ASSR application is the presence of 'hostile' characteristics inherent to the operating room, such as ambient acoustical noise and electrical interference from the necessary equipment. With specific precautions, however, these interferences can be diminished, as shown in an unpublished study in older infants from the ExpORL research group (Alaerts, 2009), where only in two out of 27 children ASSRs could not be recorded. However, time-consuming methods remain an important criticism of ASSR threshold determination in the intra-operative setting.

Latency estimation

The estimated latency can be used to determine the delay introduced by the auditory system, as this is related to the neural generators of the ASSRs. An estimation of latency is provided through the measurement of the phase of the response at different stimulus frequencies. The ASSR phase value can be converted into phase delay (in degrees), by subtracting it from 360 degrees. The conversion from phase delay into latency, however, is less straightforward (John & Picton, 2000). First, filtering can affect the measured phase. Second, because of the circularity of phase, the steady-state nature of the response makes it difficult to determine how many additional full cycles proceeded the cycle wherein the phase delay was measured. John & Picton (2000) proposed the 'preceding-cycles' technique, plotted as the best fit across different

stimulation rates: the mean latency (i.e. group delay in other research domains) is calculated as the ratio of the differences of phase delay and stimulation rate divided by 2π for corresponding measurements with different stimulation rates. For apparent latency to be meaningful the slope of this best fit must be linear and the measurement dominated by a single neural generator within the frequency range of interest. In literature, some controversy exists regarding latency calculations because of some assumptions that are made, e.g. related to multiple generators, therefore estimates should be always interpreted with caution (Picton et al, 2003).

Neural generators

The determination of neural generators plays an important role for neuro-imaging studies, as it defines the main anatomic correlate on the auditory pathway. As described in Picton et al (2003), an amplitude modulated signal activates the basilar membrane in a region specific to the carrier frequency. Inner ear cells, subject to the rhythm of the modulation, will stimulate the spiral ganglion neurons through the mechanism of a neurotransmitter release. The firing of the neurons is subject to a half-wave rectification as action potentials are only transmitted after depolarization. This results in a recorded auditory nerve activity at the modulation rate.

Many data are available and it is generally accepted that a stimulation rate in the 40 Hz frequency range generates cortical responses, and rates around 80 Hz frequency range, generate subcortical responses including the brainstem (Picton, 2011). Hence, ASSRs have gained wide acceptance for auditory temporal processing deficits in different pathologies, such as dyslexia (Poelmans et al, 2012) but also for sound localization research (for a review, see Picton, 2013). In the field of hearing implants, electrically evoked responses have been described in CI patients (Ménard et al, 2004) and introduced for the fitting of CI (Hofmann & Wouters, 2012). Although 80 Hz responses are less influenced by sleep or anesthesia (Cohen et al, 1991) and therefore potentially useful for intra-operative monitoring in case of AHI implantation, literature is currently lacking. One explanation might be that new experimental methodologies for the measurement of AEPs need to be developed first. So far, only one study has investigated the use of ASSR, as a relative measurement for the placement of an AMEI at the level of the RW (Verhaegen et al, 2010).

1.4.3 Laser Doppler vibrometry

AMEIs and DACI are designed to reproduce the deficient or absent middle ear function. Traditionally the acoustic transformer system of the middle ear is regarded as a combination of three systems overcoming the impedance mismatch between air in the external ear canal and fluid in the cochlea. The first system is the catenary lever, because of the tympanic membrane where the sound energy is directed away from the edges toward the center of the drum. Secondly, the ossicular lever is created by the joint action of the middle ear ossicles. Thirdly, the hydraulic lever is formed by the difference in area between the tympanic membrane and stapes footplate. Recent investigations have added insights regarding the ossicular coupling (referring to the frequency-dependent middle ear transfer function), the acoustic coupling (difference in sound pressures acting directly on the oval and round windows) and the stapes-cochlear input impedance (determined by the impedance of the annular ligament, the cochlear fluids, cochlear partition and the RW membrane) (Merchant et al, 1997). Many of these insights were gained through investigations on human cadaveric temporal bones, using laser Doppler vibrometry (LDV) (Voss et al, 1996) or intracochlear sound pressure measurements (Nakajima et al, 2009). With these objective tools the middle ear transfer function and cochlear mechanics can be investigated in a preclinical setting, assessing different pathologies, such as induced stapes footplate fixation (Nakajima et al, 2005). But also the performance of different implants in the middle ear can be analyzed (Rosowski et al, 2007). The principle of LDV is explained below. Anecdotally, it should be noted that other techniques, such as finite element modeling of the middle ear, are equally important for the examination of the vibro-acoustic characteristics of middle ear implants (Kelly et al, 2003).

LDV allows non-contact optical measurements of the surface of vibrating objects (Huber et al, 2001). For acoustic research, mainly single point lasers are used, directing the laser beam at the vibrating structure. With high accuracy ($< 1 \times 10^{-4}$ µm), the vibration amplitude and frequency are extracted from the Doppler shift of the reflected laser beam frequency.

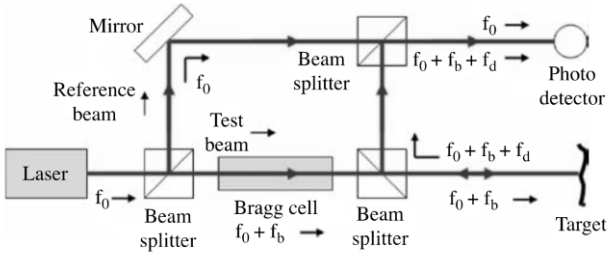

Figure 1.8 Basic components of laser Doppler vibrometry (Bogue 2010).

Generally the obtained output is a continuous analog voltage that is directly proportional to the velocity of the vibrating target along the direction of the laser beam (Goode et al, 1996). Figure 1.8 depicts the basic components of an LDV, showing the beamsplitter and photodetector, in addition to the laser, as the main components. When the laser beam hits the target, some portion of the reflected light is captured by the LDV, reflected by the beamsplitter to the photodetector. The output of this photodetector is a frequency-modulated signal. The resulting signal can be demodulated to derive the velocity vs. time of the vibrating target. In general, a multisine tone is used for stimulation (Huber et al, 2001) containing multiple frequencies between 100 Hz and 8000 to 10000 Hz, produced by a signal generator. From the measured velocity, the displacement amplitude of the vibrating structure, such as the stapes head or round window membrane, can be calculated.

For the purpose of standardization, a manual for describing the system output of AMEIs ex vivo has been published (ASTM, 2005). This 'standard practice' allows for the determination of the sound-induced stapes velocity, unaided and aided with an AMEI. It is built upon the middle ear transfer function and the linearity of the hearing system drivers, where a transfer function is the frequency-dependent ratio of the output of a device normalized by its input, as described by Rosowski et al (2007). The procedure should be regarded as an estimation of the sound pressure level based on transfer function information, as defined by ANSI 3.7 (ASTM, 2005). This transfer function is related to the real ear to coupler difference used to predict the real sound pressure level that is delivered by a transducer (i.e. hearing aid) to a subject (Dillon, 2012). The ASTM practice advises to use temporal bones of sufficient quality based on

acceptance criteria. The criterion range was deduced from a database of 13 studies by different laboratories involved in human temporal bone research (Rosowski et al, 2007).

With reflective targets on different middle ear structures, LDV allows for different velocity measurements, as shown in Figure 1.9. The ASTM method predicts the expected equivalent sound pressure level if an electrically driven system is attached to the middle ear ossicles. Comparing the sound-induced stapes velocity, H_{TV}, to the AMEI-aided stapes velocity, H_{EV}, then allows for the computation of the equivalent ear canal sound pressure transfer function, H_{ET}:

$$H_{ET} = H_{EV} / H_{TV}$$

H_{ET} is used together with the maximal electrical signal deliverable to the hearing system's transducer, E_{max}, to compute the maximum equivalent sound pressure level, $L_{E,max}$ with units of dB SPL, as in the following equation:

$$L_{E,max} = 20 \log_{10} (H_{ET} E_{max} / 2 \times 10^{-5} \text{ Pa})$$

Rosowski et al (2007) already stated before that the $L_{E,max}$ estimation assumes that H_{ET} is linear over the input range under the maximal electrical signal (E_{max}). All of the above calculations can also be applied to a DACI device. However, two important remarks related to the current PhD project should be taken into consideration. First, both the ASTM practice as well as Rosowski's work usually applies to AMEI, measured at the stapes footplate. The Codacs DACI implantation, however, removes the stapes superstructure and couples directly to the inner ear. Accordingly the system's output can only be recorded at the RW, probably resulting in a certain underestimation of the implant's performance, as noted also by Maier et al (2013). Second, so far, no standard practice for entire cadaver heads investigations has been published. In Chapter 5, entire heads were used, as they are more representative for real-life DACI implantation. Importantly, it should be remarked that LDV can only be performed intra-operatively whereas AEPS measures can be recorded both intra- (i.e. during surgery) and postoperatively.

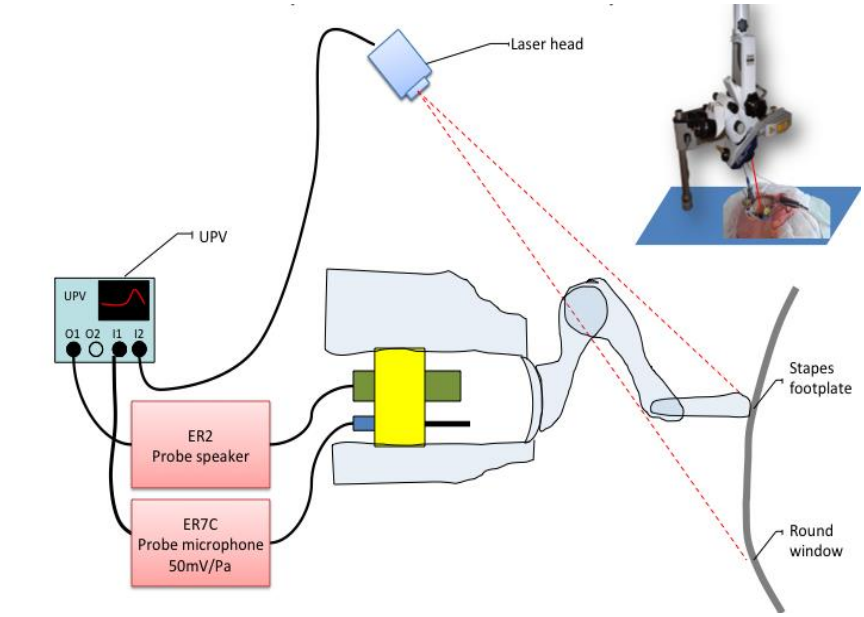

Figure 1.9 Schematic setup in cadaver head with LDV beam on targets at stapes and at RW membrane.

1.5 Behavioral and self-reported evaluation

In addition to objective measures, the outcome of a hearing rehabilitation strategy can be evaluated with clinical audiometry measuring behavioral thresholds and with a focus on the patient's self-reported appreciation. A short overview, relevant for this PhD project, of the audiological testing and patient-reported outcome measures (PROM) is provided.

Pure-tone audiometry, where the hearing threshold is determined at several frequencies important for the listener's hearing, forms the basic clinical hearing assessment. The unaided pure tone average (PTA) can be measured both for the air conduction (AC) as for the bone conduction (BC) pre- and postoperatively at several intervals. This allows determining the degree and type of hearing loss and often, taking into account the medical history and examination, its underlying cause. Both for HAs as for AHIs, aided PTA can be determined in a sound field measurement. These measurements are often performed with warble tones with the speaker positioned at 0° azimuth in

unaided and aided conditions. It is important that the contralateral ear should be adequately covered or plugged and masked. In case of severe to profound MHL of both ears, a masking dilemma can occur (Figure 1.10). Because of an important degree of inner ear hearing loss, the Weber tuning fork test is not practicable anymore. Therefore, insert phones improving the interaural attenuation can be used (Munro, 1999). Also other tests such as the Sensorineural Acuity Level test (SAL) or bone conduction ABR are worthwhile (Webb & Greenberg, 2000).

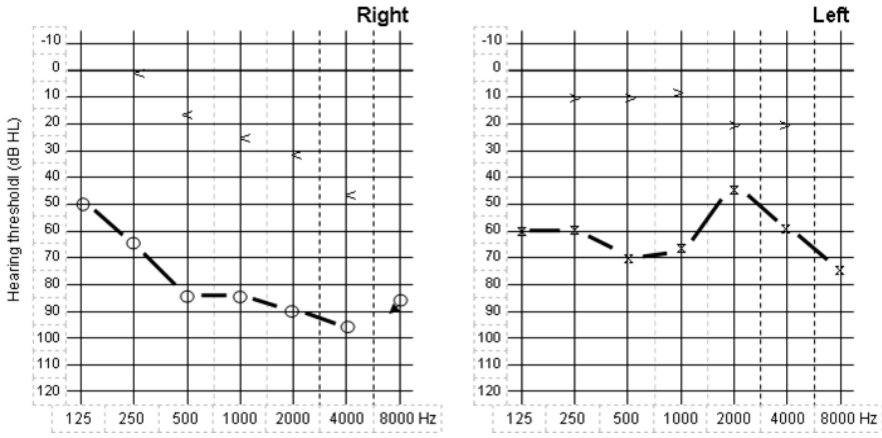

Figure 1.10 Pure tone audiometry obtained with insert phones, of a subject with masking dilemma.

Speech reception tests, analyzing the ability to perceive and recognize complex speech sounds, are more pertinent to the hearing in the daily communicative environment. Certainly important is the testing in quiet, such as the standardized monosyllabic testing, for example the NVA monosyllables in Dutch or Freiburger monosyllables in German. Word recognition scores are tested at different intensities, often at 50, 65 and 80 dB SPL. More meaningful to the real-life situation is the assessment of the communication in difficult listening condition such as background noise (Woods et al, 2010). For this purpose, the estimation of the speech reception threshold (SRT) for supra-threshold speech stimuli presented in noise is highly valuable. If listeners with an important sensorineural hearing loss would be fitted with an HA or AHI according to the pure tone thresholds alone, a more affected supra-threshold SRT in noise can be overlooked, possibly leading to the general complaint: “I can hear what

people say, but I can't understand them" (Plomp, 1978). For hearing impaired subjects, adaptive sentence tests for the assessment of speech understanding in noise are often used, with a noise level fixed at 65 dB SPL (van Wieringen & Wouters, 2008). As shown in Figure 1.11, the SRT is defined as the SNR, at which 50% of the words in a sentence are correctly repeated, most commonly done as a simple 1-up 1-down adaptive procedure, with a step size of 2 dB (Plomp & Mimpen, 1979).

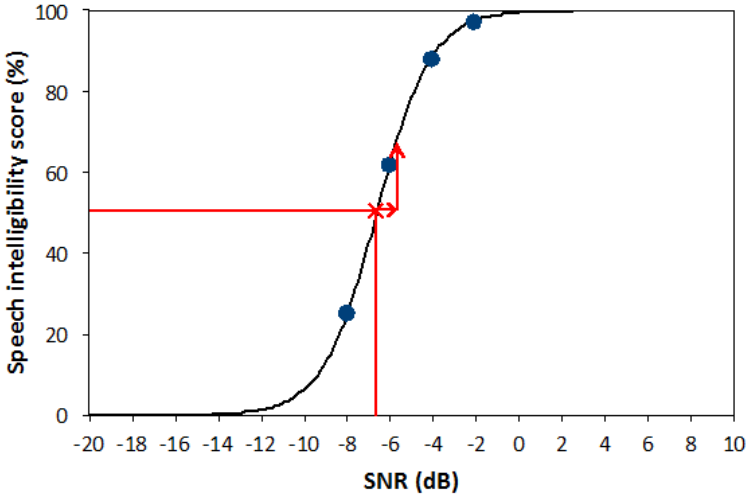

Figure 1.11 Graph represents a speech in noise testing; red line indicates the SRT.

Self-reported measures, such as the subjective assessment of a hearing system reported by its wearer, representing the disability of life, are becoming increasingly important. Notwithstanding that most patients are biased because they cannot wear HAs for several reasons, establishing functional benefits in a veritable world environment through validated standardized questionnaires is mandatory. Rapidly, with raising global pressure on healthcare budgets, these instruments measured prior to and after the implantation, are gaining importance. Many questionnaires are being used; a selection is mentioned here.

The Abbreviated Profile of Hearing Aid Benefit (APHAB) is a 24-item self-assessment inventory in which the subject reports the amount of trouble she/he is having with communication or noises in various everyday situations

(Cox & Alexander, 1995). Benefit is calculated by comparing the wearer's reported difficulty in the preoperative unaided condition to their amount of difficulty when using amplification. The APHAB produces scores of four subscales: ease of communication, reverberation, background noise and aversiveness. Higher scores reflect more communication problems.

The Health Utilities Index (HUI®) is a generic, preference-scored, comprehensive system for measuring the health status and the health related quality of life and for producing utility scores. The HUI used in 0 is a 15-item self-administered questionnaire that has been designed to ask the minimum number of questions required to classify a subject's health status.

Additionally, evaluating sound localization and spatial aspects in subjects with unilateral or bilateral hearing loss with HAs and AHIs can be performed with the questionnaire derived from the 50-item Speech, Spatial and Qualities of Hearing Scale (Gatehouse & Noble, 2004). For all these questionnaires, validated Dutch translations are available. The SSQ was translated to Dutch by members of ExpORL-KU Leuven and has been used for the evaluation of the functional benefit in percutaneous BCIs (van Wieringen et al, 2011).

1.6 Research objectives

Direct acoustic cochlear stimulation has recently been proposed as a possible treatment of MHL that may resolve power constraints of other AHIs or hearing aids. The general aims of this PhD project were 1) the audiological evaluation of the clinical application of DACI[2] in a limited number of subjects with severe to profound MHL, 2) the investigation and development of objective measures to quantify the functionality of DACI and 3) the study of optimal coupling strategies to the inner ear. These objectives are related to the more specific research questions.

The general research questions were:

1. What is, in literature, currently regarded as the evidence-based treatment of MHL?

[2] Unless otherwise specified, the DACI used and referred to in this work is the Codacs system (Cochlear Ltd).

2. What is the efficacy of a DACI in audiological terms?
3. Is it possible to develop objective measures for direct acoustic cochlear stimulation and can we reliably obtain electrophysiological thresholds in subjects implanted with a DACI?
4. Is it possible to couple the DACI at an easy accessible inner ear site and does it provide sufficient gain?

The *first* main objective comprised a complete clinical evaluation of the DACI device in subjects with severe to profound MHL. Previous studies showed beneficial speech understanding in quiet due to its powerful amplification mainly investigated in comparison to the unaided situation in a selected group of subjects with otosclerosis (Lenarz et al, 2013). Also in DACS-PI (Phonak Acoustic Implants SA, Switzerland), the first clinical results on speech understanding compared to HAs have recently been reported (Busch et al, 2013). Together with the surgical aspects, the audiological efficacy of the device needed to be investigated in a broader indication range of subjects with severe to profound MHL. Five tertiary referral centers in Europe participated in this study. As a first goal, speech understanding in quiet and certainly in noise was investigated, comparing the device to the subject's best alternative treatment. Because of its powerful amplification, it is questioned whether this new technology can improve the signal-to-noise ratio for people with MHL, especially in difficult listening conditions. Additionally, because patients are treated, we aimed to extensively evaluate the amount of difficulty experienced with communication in various everyday situations and the impact of the hearing rehabilitation on general health and hearing. Previously to this research and as guidance for evidence-based research, the current literature was reviewed extensively for results on the hearing rehabilitation of purely MHL. Special attention is needed as its treatment balances between the need to overcome middle ear function and to explore the remaining cochlear reserve, without compromising either one of them.

The *second* objective of this project was to develop and to investigate a method for the objective evaluation of the coupling of the DACI to the inner ear and the entire auditory pathway. Similar to CIs (Ménard et al, 2004; Hofmann & Wouters, 2010) we aimed to explore, in a non-invasive manner, the feasibility that ABRs and ASSRs can be evoked in response to acoustic stimulation with a

DACI, and that they are closely related to behavioral measured thresholds. Only two studies have investigated the use of auditory evoked potentials in patients with AHIs (Colletti et al, 2012; Verhaegen et al, 2010), neither of them with digital speech processing devices, nor for the absolute determination of ABR and ASSR thresholds.

As a *third* objective, the feasibility of coupling the DACI actuator to an anatomically easy accessible inner ear site was investigated in terms of acoustic performance. Surgery for DACI implantation is much alike cochlear implantation with risks of facial nerve exposure and inner ear damage. Consequently, it would be very interesting to develop an easier coupling strategy to the inner ear avoiding this exposure retaining, however, its powerful and broad spectrum output. The lateral semicircular canal (LC), being a part of the inner ear structures, is rapidly encountered when opening the mastoid cavity without the need for facial nerve exposure. For this reason, the standard coupling to the oval window was compared to different couplings at the level of the LC. Moreover, a stapes footplate fixation, as in otosclerosis, was induced artificially elucidating its impact on the DACI stimulation at the LC.

1.7 Thesis outline

In order to provide answers on the research questions raised in the previous paragraph, four studies have been carried out. The first two studies (Chapter 2 and 3) will elaborate the questions regarding the first objective, the third study (Chapter 4) regarding the second objective and finally the fourth study (Chapter 5) regarding the last.

In **Chapter 2**, a systematic review of the literature was carried out to determine the clinical outcome and safety of the whole range of AHI in adults with MHL, using the databases of MEDLINE, Embase and the Cochrane Library up to March 1, 2013. Previous work on conductive and sensorineural hearing loss solutions was excluded. The search syntax is shown in Appendix A.1. A study quality assessment was performed in the first part of this chapter. Meta-analyses could not be performed because of the heterogeneity of the studies. Therefore, in the second part, the results were presented in tables with structured review of

different outcome measures: safety, PTA, functional gain, impact of coupling, speech understanding in quiet and in noise, patient-reported measures. The content of this chapter has been published in *Otology & Neurotology* (Verhaert et al, 2013a).

Chapter 3 reports the prospective audiological evaluation of the Codacs DACI, with a focus on speech understanding in quiet and in noise, in a multicenter study. The subjects, suffering from severe to profound MHL were fitted with hearing aids and/or a bone conduction implant on a headband before DACI implantation. This allowed direct comparison between different hearing rehabilitation solutions. Safety of the procedure and the subjective benefit were assessed. The content of this chapter has been published in *Audiology & Neurotology* (Verhaert and Lenarz[3] et al, 2014).

In **Chapter 4,** the development of objective measures for direct cochlear acoustic stimulation in humans was described. By measuring auditory evoked potentials the auditory pathway could be evaluated after DACI implantation in subjects with some remaining cochlear reserve. Specific research development items were the artifacts analysis of the implant and electrophysiological threshold determination using Auditory Brainstem Responses and Auditory Steady-State Responses in three subjects implanted at the University Hospitals Leuven. The three subjects formed part of the multicenter study described in Chapter 3. The content of this chapter has been submitted to *Ear and Hearing* (Verhaert and Hofmann et al, 2014).

Another experimental investigation of direct acoustic cochlear stimulation is reported in **Chapter 5,** aiming to simplify the surgical coupling to the inner ear and to broaden the indication range**.** The feasibility of coupling the DACI device to the LC, thereby creating a 'third-window' in addition to the normal oval and round window of the human cochlea was examined. RW velocity, as a measure of the device's performance and its coupling efficiency, was determined in fresh-frozen human cadaver heads using a LDV setup. The output of the device stimulating this 'third-window', even in case of stapes footplate fixation, was compared to the standard setup. The material presented in this chapter has been submitted to *Hearing Research* (Verhaert et al, 2014b).

[3] If two names are cited, joint first authors are indicated.

In **Chapter 6**, the general findings of this PhD project are discussed and future research directions are presented.

In **Appendix A**, to conclude, the search syntax and study selection criteria of the systematic review in Chapter 2 are described. Also the protocol of the prospective multicenter study from Chapter 3 is given.

Chapter 2
Acoustic hearing implants for mixed hearing loss: a systematic review[4]

2.1 Abstract

Objective: A systematic review of literature to determine the clinical outcome and safety of the range of acoustic hearing implants (AHIs) in adults with mixed hearing loss (MHL). **Data sources:** Databases MEDLINE, Embase and Cochrane were searched with no language restrictions between 1950, or the start date of each database, up to March 1, 2013. **Study Selection:** Initial search found 1794 studies, of which, 19 met the inclusion criteria of AHI for adults with MHL where safety, coupling strategies to the inner ear, hearing outcome and patient-reported outcome measures (PROMs) were analyzed, preferably compared to a conventional hearing aid or a bone-conduction implant. **Data extraction:** A study quality assessment based on different parameters was included: specification of eligibility criteria, prospective study, ethical approval gained, appropriate controls, power calculation, outcome measures, and analysis performed. **Data synthesis:** Comparisons between studies were made based on structured review, as meta-analysis was not feasible because of the heterogeneity of outcome measures and reports. **Conclusion:** The current systematic review shows that AHIs and their different coupling strategies in the treatment of MHL were beneficial in terms of speech in quiet, PROM and safety regarding residual hearing. Overall, the level of evidence and the quality of the included studies was judged to be moderate to low. More comprehensive data on coupling to the inner ear and the comparison with conventional hearing aids

[4] The content of this chapter has been published as: Verhaert N., Desloovere C., Wouters J. 2013. "Acoustic hearing implants for mixed hearing loss: a systematic review." In: *Otol Neurotol*, 34:1201–9.

or alternatives for speech in noise is mandatory. Long-term follow-up data are also needed. **Level of evidence:** 3a

2.2 Introduction

Mixed hearing loss (MHL) is defined as a combination of conductive and sensorineural hearing loss. Different degrees of severity of MHL can be caused by several pathologies. One of them is otosclerosis, a disease characterized by lesions in the endochondral bone of the otic capsule (Chole & McKenna, 2001). A 'cochlear' otosclerosis is associated with sensorineural hearing loss. It has been estimated that 1.6% of patients with otosclerosis will eventually develop profound sensorineural hearing loss (Shea et al, 1999). A second pathology possibly resulting in MHL is chronic otitis media. Because of inflammation associated with, for example, tympanic membrane retraction, cholesteatoma or previous surgery, both conductive as sensorineural hearing loss can occur. Poor hearing outcome has been explained by absent or diminished ventilation of the middle ear space, prosthesis extrusion, tympanosclerosis, scar tissue, tympanic membrane lateralization and eroded or missing ossicles, even after proper placement of passive middle ear implants such as total or partial replacement prostheses (TORP or PORP) (Linder et al, 2009). Often in chronic otitis media cases with sequelae at the tympanic membrane (perforations or tympanosclerosis) or large open cavities, the use of conventional hearing aids (HAs) is problematic and unsatisfactory.

Morphological abnormalities like congenital malformations could present themselves with MHL, even if conductive hearing loss is more frequent. The incidence of aural atresia is about 1:10000 births (Melnick et al, 1979). Other more seldom causes of MHL are associated with trauma; labyrinthine contusion and temporal bone fracture with stapes footplate fracture have been described.

Over the last years, conventional HAs, although remarkably improved, have not always been able to overcome certain anatomical and hearing loss issues, as mentioned above. Acoustic hearing implants (AHI) can be divided in active and passive implants, whether the function of the implants depends on external energy or not. Currently, these AHI cover the broad range of mostly passive

bone-conduction implants, such as osseointegrated bone-conduction implants (BCI, formerly Bone-Anchored Hearing Aid (BAHA)), to active middle ear implants (AMEI) and direct acoustic cochlear implants, named DACI or DACS depending of the source of publication.

Passive osseointegrated BCI could partially overcome the sensorineural hearing loss up 40 to 50 dB HL, as shown with the body-worn Baha Cordelle (Bosman et al, 2006). Substantial work comparing outcome of passive bone-conduction implants in severe MHL with matched HA controls have been performed by the Nijmegen group (Mylanus et al, 1994). Initially, certain AMEIs were thought to be an alternative to HA in sensorineural hearing loss for different reasons. A systematic and comprehensive review of the safety and benefit of AMEI for sensorineural hearing loss was performed by Tysome et al (2010). AMEIs are now approved for use in conductive and mixed hearing losses (Verhaert et al, 2011). Snik et al (2004) evaluated the outcome of two electromagnetic AMEI. For the heterogeneous group of pathologies causing MHL different strategies for hearing rehabilitation have been proposed, some even as a combination, for instance, like TORP with AMEI (Beleites et al, 2011). Recently a new hearing implant has been introduced for severe to profound MHL, namely, the DACI system (Bernhard et al, 2006). An artificial actuator is coupled to a stapes piston within the vestibule, driving directly the cochlear fluids. Finally, the use of cochlear implants (CIs) for profound MHL, as seen in far advanced otosclerosis, has been described comprehensively before (Merkus et al, 2011).

With the rise of new AHI solutions and, more importantly, new coupling strategies to the inner ear, an evidence-based overview for clinical use and decision-making is mandatory. By applying robust methodology to different studies of variable quality, a systematic review enables to evaluate the effectiveness of AHI in MHL. Different applications, coupling systems and their respective safety can be explored by analyzing the reported complication rate and the impact on residual sensorineural hearing. The efficacy of AHI in terms of functional gain, speech understanding in quiet and noise and PROM will be investigated.

2.3 Methods

This review was reported in accordance with the Preferred Reporting Items for Systematic reviews and meta-analyses statement (Moher et al, 2009).

2.3.1 Search strategy

A systematic review of the literature was conducted, without language restrictions, using the databases of MEDLINE (PubMed), Embase (based on EMTREE terms), and the Cochrane Library up to March 1, 2013. Search syntax is shown in Appendix A1.

2.3.2 Study selection

Studies were judged for inclusion if they fulfilled the criteria as determined in Appendix A2. All studies were assessed by reading title and abstract, then by retrieving the full article, hereby making the final selection based on the inclusion criteria. References and related articles were screened to verify if all valuable articles were included. Case reports, reviews and editorials were excluded.

2.3.3 Data extraction

Data was extracted from the included studies using standardized formats incorporating the following variables: number of patients, type of pathology, type of AHI, coupling to inner ear, time of follow-up, outcomes and level of evidence. The level of evidence was assessed according to the criteria of the Centre for Evidence-Based Medicine (University of Oxford), in agreement with the Belgian *Centre* for *Evidence-Based Medicine,* a branch of the Cochrane collaboration (Oxford Centre for Evidence-Based Medicine, 2009).

Outcomes were recorded in terms of initial mean bone conduction (BC) thresholds determining the severity of inner ear damage, complications of procedure, functional gain, speech understanding in quiet and in noise and validated PROM questionnaires. Many variables and formats have already been suggested by Tysome et al (2010).

2.3.4 Methodologic quality

The quality of studies was assessed based on different categories: ethical approval, prospective study, eligibility criteria specified, a power calculation made, appropriate controls and outcome measures used, confounding factors reports and controlled for, appropriate analysis made, and any missing data accounted for (Tysome et al, 2010).

2.3.5 Devices

In this review several types of implantable hearing solutions are included: CI, osseointegrated bone-conduction implant (BCI) such as BAHA (Cochlear Bone Anchored Solutions AG, Mölnlycke, Sweden), Vibrant Soundbridge (VSB) and its floating mass transducer, FMT, (MED-EL, Innsbrück, Austria) and Otologics with its Middle Ear Transducer (MET-V, Otologics & Cochlear™, Boulder, CO, USA). Direct acoustic cochlear implantation, with the DACI system, has been described in previous reports (Bernhard et al, 2006; Häusler et al, 2008). As all devices have been described exhaustively previously, no additional description is provided in this review.

2.4 Results

2.4.1 Study selection and characteristics

Figure 2.1 shows a flow chart of study selection process. Nineteen studies met the inclusion criteria, and 11 studies were excluded because only joint data on MHL and conductive hearing loss were presented and no separate analysis was performed, for example in Mylanus et al (1994) or in Verhaert et al (2011). Other, although valuable, studies showed nonextractable data because missing standard deviations or raw data, for example in the study of Lachance et al (2012). Many studies had different setup or outcome measures, making them unsuitable for comparison in this systematic review.

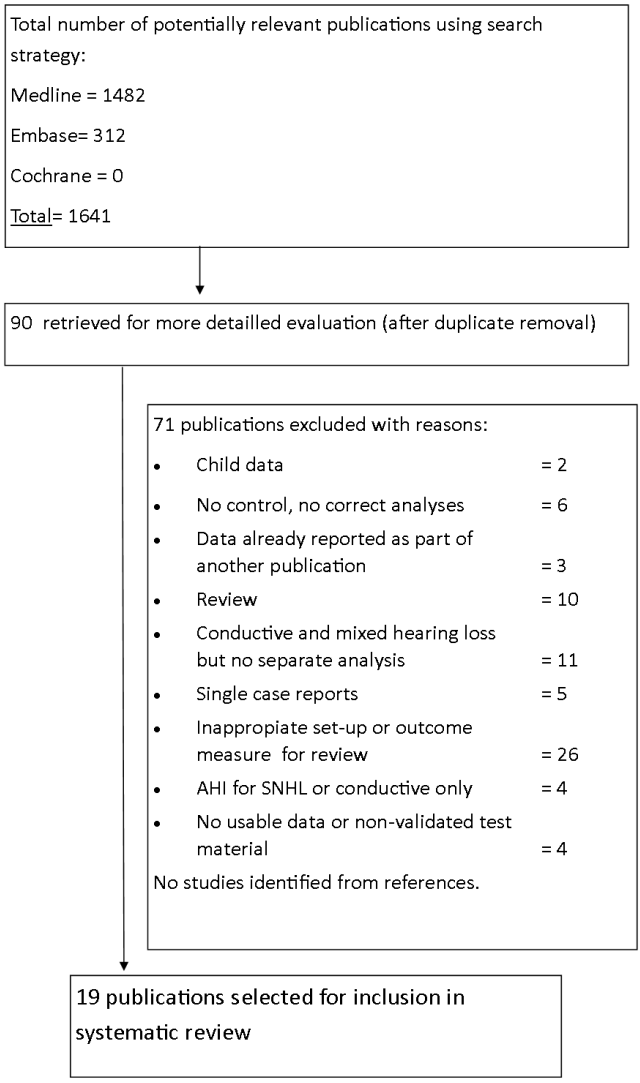

Figure 2.1 Flow chart of study selection.

In all but 1 study, patients served as their own controls. Verhaegen et al (2012) represents the exception, as a group of hearing-matched patients with BCI and a group of sensorineural hearing loss patients with AMEI were chosen for comparison. Table 2.1 summarizes the characteristics of each included study. Speech tests in quiet were recorded in English, German, French, Italian, Dutch

and Cantonese. In some languages, both monosyllabic and disyllabic words were used. PROM was mainly assessed by the Abbreviated Profile of Hearing Aid Benefit (APHAB) questionnaire (Cox & Alexander, 1995), some also used the Glasgow Benefit Inventory (GBI) and the Hearing Device Satisfaction Scale (HDSS).

2.4.2 Methodological quality of studies

Neither a randomized controlled trial, nor a cross-sectional study was included. Figure 2.2 provides an overview of the different categories mentioned in the Methods section. It shows that only 21% of the studies were prospective cohort studies. Follow-up ranged from 6 weeks to 48 months. Seven studies reported on PROM.

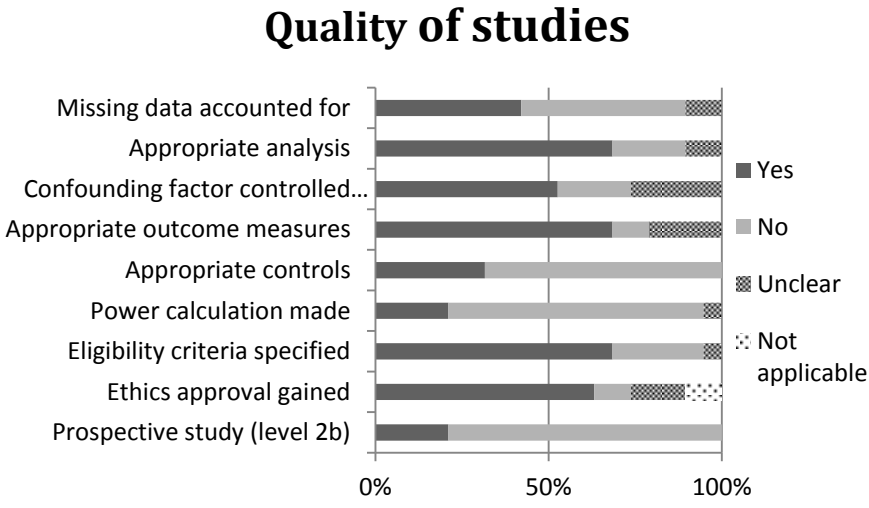

Figure 2.2 Quality of studies included.

Many study protocols described correctly the patient selection criteria. Contrastingly, the results were not fully described in the text and confounding factors rarely addressed. Although comparison to alternatives, such as HA or TORP is not feasible for each pathology or subject, only few studies addressed this comparison.

Table 2.1 Characteristics of studies.

Study	No. of Patients	Type of patients/disease	MEI/BCI	Coupling	Controls	Outcome measures	Follow-up /mo	Level of evidence
(Streitberger et al, 2009)	40	COM n=20 / cholesteatoma n=20	VSB	32 RW; 5 stapes footplate; 2 stapes head; 1 Coch.	Own (no HA)	PTA bisyllabic words Italian Freiburger	6-9	3b
(Bosman et al, 2006)	25	COM	BAHA Cordelle	NA	No	PTA CVC-syllables	Not stated	3b
(Colletti et al, 2006)	7	COM	VSB	RW (no fascia)	Own (no HA)	PTA Bisyllabic words	9	4
(Häusler et al, 2008)	4	otosclerosis	DACS	piston	HA	PTA Freiburger Fournier Basler (SPIN)	24	3b
(Böheim et al, 2012)	12	3 COM, 6 chole, 2 tympano-sclerosis, 1 unknown	VSB	RW- no coupler	Own (preop unaided)	PTA Freiburger OLSA APHAB	31-46	3b
(Schwab et al, 2012)	3	1 failed stapedotomy, 2 cholesteatoma	VSB	TORP – OW	Own (preop unaided)	PTA Freiburger OLSA APHAB HDSS GBI	3-6	3b
(Yu et al, 2012)	8	7 COM, 1 cholesteatoma	VSB	6 RW ; 2 stapes head	Own (previous HA in n=6)	PTA CHINT in quiet and noise	6	2b
(Verhaegen et al, 2012)	6	2 radical cavity, 1 COM, 3 OE with failure of VSB-incus	VSB	5 stapes head; 1 RW	BAHA and VSB for SNHL	PTA CVC-words APHAB	19-48	3b
(Beleites et al, 2011)	14	2 CAA, 9 COM or OE	VSB-TORP/PORP	9 TORP (OW coupler); 5 Clip-coupler on stapes head	Own (no HA)	PTA Freiburger	not stated	4
(Kontorinis et al, 2011)	2 (3 ears)	2 otosclerosis + OE	VSB-piston	stapes prothesis	Own (HA)	PTA Freiburger	12	4
(Orús Dotú et al, 2011)	12	COM , 1 cophosis	Baha Cordelle	NA	No	PTA Speech recogn. Not specified	6	4
(Martin et al, 2009)	11	3 otosclerosis, 8 COM	MET – Carina	Ball prosthesis on RW (+ fascia)	Own	PTA Fournier, Spanish word lists APHAB	12-24	4
(Colletti et al, 2009)	38	bilateral COM	TORP vs VSB-RW	fascia on RW	TORP vs RWI	PTA Italian bisyllabic words	36	3b
(Linder et al, 2009)	5	COM	VSB	RW + fascia	Own (no HA)	PTA Freiburger GBI	> 24	4
(Rajan et al, 2011)	10	7 COM, 1 cochlear otosclerosis	VSB (≠coupling strategies)	RW (4 with fascia);2 drop-out	Own (no HA)	PTA Artur-Boothroyd word lists, adaptive BKB SPIN APHAB	12	2b
(de Wolf et al, 2011)	16	COM	Baha Intenso	NA	HA	PTA Speech in quiet, Plomp sentences APHAB	1.5	3b
(Bernardeschi et al, 2011)	25 (29 ears)	18 COM, 6 otosclerosis, 3 CAA, 2 stenosis MAE	VSB	16 on incus; 10 on RW (+fascia); 3 on stapes	Own (no HA)	PTA Fournier (mono)	mean of 8 (2-28)	4
(Beltrame et al, 2009)	12	7 CSOM, 4 otosclerosis, 1 CAA	VSB	RW (no fascia)	Own (no HA)	PTA, Italian – Freiburger, OLSA	7-9	4
(Verhaert et al, 2013b)	16	COM (+/- cholesteatoma)	VSB	13 RW (5 coupler); 1 OW coupler; 2 stapes	Own (BAHA/HA)	PTA Freiburger	≥ 6	4

NA indicates not applicable; COM, chronic otitis media; CAA, congenital aural atresia; OE, otitis externa; RW, round window; OW, oval window; TORP, total ossicular replacement prosthesis; Coch., cochlear fenestration; SPIN, speech in noise test, BKB, Bamford-Kowal-Bench test; OLSA, Oldenburger sentences test (in noise); CVC, consonant-vowel-consonant lists. Other abbreviations see p. 16

Statistical comparison of the data is rendered difficult due to the small size of many of these studies. Meta-analyses could not be performed due to the heterogeneity of the studies. Therefore, similar as in Tysome et al (2010), the results are presented in tables with structured review. Rating the quality of these studies coherently was difficult because of the different study design and risk of bias; hence we divided them quantitatively. Two studies reported all categories of outcome measures specified in this review (de Wolf et al, 2011; Rajan et al, 2011). Nine studies reported between 5 and 8 categories, respectively, 8 under 5 categories.

2.4.3 Outcome measures

Safety Complications were reported in 11 of the 19 articles (Table 2.2). One device failure was noted with the totally implantable MET system, 1 with the VSB system. Several TORP extrusions were noted in the comparative study of Colletti et al (2009). Respectively 3 VSB and 2 MET explantations were reported in the included studies. In general, most problems occurred in repositioning the FMT because of insufficient gain.

Pure tone audiogram In most, but not all, studies the mean PTA was calculated according to AAO-HNS criteria (averaging the AC and BC pure tone thresholds at 0.5, 1, 2, 3 kHz). In general, residual hearing stayed unchanged, as shown in Table 2.3. Häusler et al (2008) measured an improvement of BC mainly at the Carhart notch. Two studies reported a deterioration of BC after the procedure: Linder et al (2009) noted a BC loss at 2 kHz of 10 to 30 dB after subtotal petrosectomy and VSB implantation. Colletti et al (2006) reported a mean BC threshold loss of 5 to 7 dB when placing a FMT to the round window (RW). Three studies did not specify the residual hearing; 2 out of these 3 were BCI procedures with no supposed risk to the inner ear.

In 13 of the 19 studies, the mean preoperative BC was clearly cited. This varied between 38 and 53 dB HL with a median value of 39 dB HL, showing a moderate to severe hearing loss. Some subjects of the included studies had profound MHL, mainly in the studies of Bosman et al, (2006) and Häusler et al (2008).

Table 2.2 Complications of acoustic hearing implant in mixed hearing loss.

Study	No. Of patients	Device	Complications
(Häusler et al, 2008)	4	DACI	1 temporary dysgeusia
(Böheim et al, 2012)	12	VSB-RW	1 FMT displacement; 1 recurrent cholesteatoma
(Schwab et al, 2012)	3	VSB-TORP	None
(Kontorinis et al, 2011)	2	VSB-stapes	Bleeding intra-operatively
(Orús Dotú et al, 2011)	12	BCI	3 partial flap necrosis; 1 skin overgrowth
(Martin et al, 2009)	11	MET	2 explantations due to infection; 1 SNHL; 1 device failure
(Colletti et al, 2009)	38	TORP versus VSB-RW	2 TORP extrusions, 2 TORP revision surgery for poor result; 2 VSB explantations: 1 for insufficient gain, 1 for device failure
(Linder et al, 2009)	5	SP + VSB-RW	1 retro-auricular wound infection; 1 system noise
(Rajan et al, 2011)	10	VSB-RW	1 explantation for infection; 1 inner ear damage; 3 FMT repositioning
(Bernardeschi et al, 2011)	25	VSB	2 revisions for FMT displacement at RW; 1 revision for stapedotomy with vertigo
(Verhaert et al, 2013b)	16	SP + VSB-RW, -stapes	4 wound healing problems; 1 additional hearing loss

SP, subtotal petrosectomy; FMT, Floating mass transducer, SNHL, sensorineural hearing loss.

Functional gain There was no uniform definition of the functional gain with AHI in the included studies. This renders results difficult to compare. Table 2.3 provides the mean gain in dB when reported; for some studies, the range was given, depending on the frequency. Many authors defined functional gain as the improvement in PTA or in speech perception aided versus unaided preoperatively, some even postoperatively. In 3 studies, the gain was stated as an improvement over BC thresholds in aided condition. Bosman et al (2006) reported 1.5 dB gain at 0.5 kHz, 17.8 dB at 2 kHz; Colletti et al (2006) 0 (at 0.5Hz) to 20 dB (higher frequencies); Beltrame et al (2009) described a mean gain of 12 dB on 2 kHz, but less at 0.250 and 0.5 kHz. Häusler et al (2008) stated the gain in terms of improvement with the DACI system activated versus HA with stapedotomy, showing an average improvement of 7.5 dB PTA for the first.

Impact of coupling As shown in Table 2.1, 17 of the 19 studies provide details on the coupling to the middle or inner ear structure. In total, 155 subjects were implanted at the RW site, with or without coupler or fascia. Most of them were implanted with a VSB, 11 with a MET coupled to a ball prosthesis. Furthermore 24 FMT's were coupled to the stapes suprastructure or footplate, 13 to an oval window coupler. Three FMT and 4 DACI devices were coupled to a stapes piston.

Speech understanding in quiet Table 2.3 gives a detailed overview of speech reception scores in quiet. Because to different speech material, an overall comparison of the study results is impossible. Kontorinis et al, (2011) compared rigorously outcomes to the preoperative HA-aided speech reception. A significant improvement of speech in quiet scores was noted when aided with VSB and stapes prosthesis in comparison to preoperatively aided situation with HA. In a study of Colletti et al (2009), a cohort-controlled study showed a statistical significant difference between a group of subjects aided with a RW-VSB compared to subjects helped with a TORP alone, stating an aided speech reception score in quiet (at 65 dB HL, sic) of 86.2% (Standard deviation, SD = 36.5) and 22.1% (SD = 11.3), respectively. Häusler et al (2008) compared the postoperative sound field results, showing an average improvement of 7.5 dB PTA for the DACI system in comparison to HA with stapedotomy.

Speech understanding in noise As shown in Table 2.3, none of the included publications compared AHI versus HA in noise. Six of the 19 included studies tested speech understanding in noise and compared this to the preoperative or postoperative unaided condition. de Wolf et al (2011) found a significant correlation between speech in noise scores and the air-bone gap, concluding that above an air-bone gap larger than 30 to 35 dB signal-to-noise ratio (SNR) were better with an osseointegrated BCI than with HA, but no mean values for the cohort were provided. Häusler et al (2008) reported on 50% speech understanding in noise in 2 subjects showing a significant improvement compared to the unaided condition. Yu et al (2012) showed a significant SNR improvement of 2.8 dB at noise in front. Rajan et al (2011) showed significant improvement in percentage correct using BKB sentences test. Böheim et al (2012) noted a statistically significant improvement of SNR ranging from 10 dB

preoperatively to 5 dB over 40 months of follow-up. Finally Beltrame et al (2009) reported a SRT 7 to 13 dB greater than normal-hearing controls.

Table 2.3 Audiological outcome of acoustic hearing implants in mixed hearing loss.

Study	AHI	Functional gain on PTA (unaided vs aided)	Mean BC	Residual hearing	Speech perception in quiet vs control	Speech perception in noise vs control
(Streitberger et al, 2009)	VSB	30	44	=	++	not done
(Bosman et al, 2006)	BCI	NS	54	NA	NS	not done
(Colletti et al, 2006)	VSB	[10-40]	37	↓ 5 à 7 dB HL	++	not done
(Häusler et al, 2008)	DACI	51	NS	>	++	++ (n=2)
(Böheim et al, 2012)	VSB	[15-43]	NS	=	++	++
(Schwab et al, 2012)	VSB	36 [24-48]	35	=	++	not done
(Yu et al, 2012)	VSB	11*	39	=	++	++
(Verhaegen et al, 2012)	VSB	[0-28]**	NS	=	=	not done
(Beleites et al, 2011)	VSB	26	45	=	++	not done
(Kontorinis et al, 2011)	VSB	37 [33 – 44]	47	=	++	not done
(Orús Dotú et al, 2011)	BCI	46	51	=	++	not done
(Martin et al, 2009)	MET	29	NS	=	++	not done
(Colletti et al, 2009)	VSB vs TORP	58 (SD=39) vs 10 (SD=14)	NS	NS	++	not done
(Linder et al, 2009)	VSB	40	NS	↓ 2kHz 10-30 dB	++	not done
(Rajan et al, 2011)	VSB	NS	NS	NS	NS	++
(de Wolf et al, 2011)	BCI	NS	38	=	+	=
(Bernardeschi et al, 2011)	VSB	24	42	=	+	not done
(Beltrame et al, 2009)	VSB	38*	44	=	++	++
(Verhaert et al, 2013b)	VSB	33	38	=	++	not done

In comparison to control: ++ indicates significant positive outcome; + positive outcome (not significant or no significance reported); = no difference; - negative outcome (not significant or no significance reported). NS= not stated or calculated; NA= not applicable; vs= versus. * compared to postoperative unaided values; ** 2 non-users.

Self-reported measures Table 2.4 provides an overview of the results obtained with different questionnaires, as investigated by 7 of the 19 studies. Six studies reported on APHAB, 2 on GBI and 1 on HDSS. Overall, APHAB scores show a significant improvement in ease of communication, reverberation in 5 of 6 studies, and for background noise in 4 of 6. Overall, aversiveness did not change significantly. GBI showed a positive impact on the general benefit. In the study of Linder et al (2009), the combined effect of the middle ear exclusion and the VSB application was evaluated.

Table 2.4 Validated patient-reported outcome measures (questionnaires).

Study	No. Of patients	Device	APHAB	HDSS	GBI
(Häusler et al, 2008)	4	DACI	++EC, ++RV, ++BN, -AV in 1 pt, +AV in 1 pt		
(Böheim et al, 2012)	12	VSB	++EC, ++RV, ++BN, -AV	++	++ general, = social and physical
(Yu et al, 2012)	5	VSB	=		
(Martin et al, 2009)	7	MET	++EC, +RV , =BN , -AV		
(Linder et al, 2009)	5	VSB in subtotal petrosectomy			+ general, +physical, = social
(Rajan et al, 2011)	10	VSB – RW	++		
(de Wolf et al, 2011)	16	BCI vs HA	++EC, ++BN, ++RV if ABG > 37-47dB; =AV		

In comparison to control: ++ indicates significant positive outcome; + positive outcome (not significant or no significance reported); = no difference; - negative outcome (not significant or no significance reported). If case is empty test was not performed. APHAB, Abbreviated profile of hearing aid benefit; EC, ease of communication; RV, reverberation; BN, background noise; AV, aversive sounds; HDSS, Hearing device satisfaction scale; GBI, Glasgow Benefit Inventory; pt, patient.

2.5 Discussion

This systematic review provides a current overview of published studies on the effectiveness of treatment of mixed hearing loss with AHI. Most studies appear moderate to low in evidence and mainly focus on precomparison and postcomparison with the subject acting as its own control, mainly unaided. Because of the heterogeneity of the studies, a meta-analysis could not be performed. An initial hypothesis of this systematic review was the question

whether AHIs and more specifically AMEIs, improve as much as conventional HAs. Due to a lack of comparative studies, as in the review of Tysome et al (2010), the focus was laid on different gains, safety, improvement in speech understanding and patient-reported outcome measures. Solely based on the results in the current systematic review, an implementation in daily clinical practice remains difficult. In this systematic review, data on children were not included. Much of the data, however, could be extrapolated.

A general remark is whether active and passive AHI should be assessed separately. The authors feel that, based on the hypothesis of this study, they should be assessed jointly, as BCI and AMEI could be considered as alternatives in different pathologies of MHL and are used likewise in the daily clinical practice.

Safety Most included publications have provided data on residual hearing. Only few deteriorations are noted. Taking into account the challenging pathology of chronic otitis media, advanced otosclerosis and congenital malformations, AMEI seems considerable as an alternative to safer procedures, like HA or osseointegrated BCI, at least in experienced hands. Tysome et al (2010) concluded that AMEIs were safe to implant for sensorineural hearing loss, based on his systematic review. Naturally spoken, longer follow-up period is needed: here, only 2 studies provide follow-up data longer than 2 years (Linder et al, 2009; Böheim et al, 2012)(Böheim et al, 2012; Linder et al, 2009). Two more studies followed their subjects up till 2 years (Häusler et al, 2008; Martin et al, 2009). Two studies addressed in detail the safety of AHI surgery in combination to a history of cholesteatoma (Linder et al, 2009; Verhaert et al, 2013b). Based on their suggestions and because of the incompatibility of follow-up with MRI for most current AHI, a staged procedure in case of possible recurrence of cholesteatoma with first-stage middle ear cleft exclusion plus obliteration and in second-stage AHI implantation seems advisable.

Functional gain Regarding outcome, comparison remains difficult because of different speech material, speech testing (both in quiet and in noise), and reporting. Some studies report the improvement in SRT, others the

improvement in percentage correct. Also few studies compared preoperative best-aided condition with HA or BCI. Colletti et al (2009) compared RW implantation versus TORP and showed a statistically significant difference in improvement between both groups postoperatively in speech understanding in quiet. They stated the need for additional gain in nonventilated or scarred middle ears. Some interesting studies on the outcome of older osseointegrated BCI types, such as the study performed by Mylanus et al (1994) on BAHA HC220, were not included in this review due to difficulty in comparing their results to current speech in noise data and the lack of functional gain data.

It is a well known fact that most governmental reimbursement authorities focus on cheaper alternative treatments. Therefore, a comprehensive comparison determining the benefit not only in terms of speech understanding in quiet and noise both also in terms of PROM and disability of life score is needed if considering the most adequate treatment of MHL. Another important factor remains that different pathologies can have different outcomes. Most subjects have undergone several surgeries and were most probably not helped with classic middle ear surgery, HA or even BCI. Obviously this creates a selection bias. On the other hand if HAs are not possible, comparison remains difficult. Similar to some studies, future studies should compare both PROM as functional results to HA or the best-aided condition. As stated before, acoustic hearing implants, such as AMEI, BCI and DACI, can be considered as a relatively safe and effective treatment option particularly for patients who could not achieve sufficient benefit with an HA or conventional middle ear surgery.

Impact of coupling Different strategies for coupling an amplifier to the middle and inner ear structures have been described in the included studies. So far, numerous data are lacking to perform comparison between different sites and materials of coupling, but the number of studies increases. In the study of Streitberger et al (2009), a subject with a fixed stapes and inaccessible RW, received coupling of the FMT to a 'third-window' by cochlear fenestration. Kontorinis et al, (2011) provide evidence of a significant improvement compared to the preoperative HAs with a so-called 'power-stapes', a combination of a classic stapedotomy with clipping of the FMT on the subject's own incus. Apart from the study of Häusler et al (2008), there is a lack of studies

comparing stapedotomy plus HA versus stapedotomy plus AMEI, most likely because of ethical reasons.

An interesting finding remains the presence of fixation of the stapes footplate. Both experimental as clinical data on the effect of coupling to a fixed stapes have been reported (Verhaert et al, 2011; Devèze et al, 2010). Some authors perform a RW vibroplasty, others a clipping of the VSB on to the fixed stapes. The obtained results remain variable and some even with limited benefit. Therefore, some authors have advocated performing a stapedotomy with direct acoustic cochlear stimulation (Schwab et al, 2012). So far, this direct coupling to the inner ear has been described in two clinical studies: Häusler et al (2008) described the coupling of a DACI transducer to a stapes prosthesis, through a fenestration hole, in 4 patients with otosclerosis. Schwab et al (2012) described the coupling of a FMT to a TORP through a fenestration hole into the vestibule in 3 patients, two of them with stapes fixation because of former cholesteatoma pathology. Based on the published data at the time of this systematic review, one could conclude that direct cochlear stimulation remains still experimental, although in experienced hands, the results seem encouraging.

Speech understanding Böheim et al (2012) mentioned an stable improvement from 10 dB SNR preoperatively to 5 dB SNR at an average follow-up of 40 months. This study examined the same study cohort as in the article of Baumgartner et al (2010) but with longer follow-up. Similar trends were observed, but there was no significant difference between 3 months postoperatively and 40 months. (de Wolf et al, 2011) described a better speech in noise understanding with an osseointegrated BCI compared with an HA if an air-bone gap above 30 to 35 dB was present. Gunduz et al (2012) compared the preoperative use of HA with VSB application on middle ear windows postoperatively, expressing functional gain in PTA and in speech discrimination scores. They found better functional outcomes with VSB than with HA. However, speech understanding with VSB and HA was similar. Unfortunately, this study could not be included in the current review because no separate analysis was made for conductive and mixed hearing loss, biasing the comparison to other studies.

Self-reported measures Most studies showed a marked satisfaction and better quality of life with little impact on the aversiveness scale. Again, it must be stressed that most of included subjects could not wear HA for several reasons, so selection bias is evident. Only 2 studies compared patient's satisfaction with AHI to HA. Yu et al (2012) showed no statistical significant different based on the APHAB subcategories. de Wolf et al (2011b) showed statistically significant improvement with BCI over HA in case of an air-bone gap above 30 to 35 dB in 3 subcategories: ease of communication, background noise and reverberation.

Quality of studies and assessment On the one hand, this review was biased toward VSB as the search retrieved more data on VSB; on the other hand this finding seemingly reflects the current clinical daily use. Pure conductive hearing loss was excluded. Speech in noise testing was poorly reported and complication rates seemed incomplete in some studies. Another minor factor that could not be controlled for was the different types of HA. Seven studies reported a number of treated subjects lower than 10, lacking strong evidence. Finally, to some extent like in the review of Tysome et al (2010), no studies stratified data for analysis based on confounding factors, like duration of deafness or severity of hearing loss, number of previous surgery or type of pathology.

2.6 Conclusion

Acoustic hearing implants, such as AMEI, BCI and DACI are increasingly applied in mixed hearing loss. Use of Vibrant Soundbridge and osseointegrated BCI seems reliable based on long-term data, although the coupling mechanisms with AMEI still need longer follow-up data. Based on functional outcome and subjective parameters, reports indicate that selected subjects gain good benefit from AHI as a relatively safe and effective treatment option. More comparative data, based on PROM and speech in noise, and adequate controls to the best-aided condition are needed for adequate assessment of the benefit in terms of functional hearing.

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Chapter 3
A comparative study on speech in noise understanding with a direct acoustic cochlear implant in subjects with severe to profound mixed hearing loss[5]

3.1 Abstract

Objective: The aim of this study was to investigate the efficacy of a direct acoustic cochlear implant (DACI) for speech understanding in noise in patients suffering from severe to profound mixed hearing loss (MHL) due to various etiologies compared to the preoperative best-aided condition. The study was performed at five tertiary referral centers in Europe (Belgium, Germany, Poland and Spain). Nineteen adult subjects with severe to profound MHL due to (advanced) otosclerosis, ear canal fibrosis, chronic otitis media, tympanosclerosis or previous cholesteatoma, were implanted with a Codacs DACI combined with a conventional stapes prosthesis. Unaided and aided speech reception scores in quiet and in noise, preoperative and postoperative air and bone conduction thresholds and aided and unaided sound field thresholds were measured prospectively during the study. Subjective benefit analysis was determined through the Abbreviated Profile of Hearing Aid Benefit (APHAB) questionnaire. Quality of life was measured by the Health Utilities Index (HUI). All subjects were fitted preoperatively with hearing aids and/or a bone conduction implant on a headband before DACI implantation. This allows

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direct comparison between different hearing rehabilitation solutions. The mean speech reception threshold in noise improved significantly by 7.9 dB signal-to-noise ratio (SNR) after activation of the DACI compared to the preoperative best-aided condition. For all 19 subjects, a mean postoperative aided speech reception threshold of 2.6 dB SNR (standard deviation = 8.3) was measured. On average, no significant shift in the bone conduction thresholds was noted 4-5 months after implantation. A mean sound field threshold improvement of 46 dB and 16 dB was measured compared to the preoperative unaided and best-aided condition, respectively. Speech reception tests in quiet showed a mean improvement of the word recognition scores by 65% and 48% at 65 dB SPL compared to the preoperative unaided and best-aided condition, respectively. In summary, DACI provides an effective improvement of the speech reception in noise compared to the best-aided condition in subjects suffering from severe to profound MHL.

3.2 Introduction

Severe to profound mixed hearing loss (MHL) remains a challenge for adequate hearing rehabilitation. Conventional hearing aids (HAs) have to overcome the air-bone gap and compensate for the sensorineural hearing loss component, possibly leading to feedback, sound distortion and output saturation issues (Verhaegen et al, 2012). In profound MHL, amplification remains insufficient for adequate speech understanding. Ear canal problems, such as ear canal infections or ear canal fibrosis, could complicate their application even more. Passive percutaneous bone conduction implants (BCIs) can overcome MHL with a sensorineural hearing loss component of up to 50 dB (Bosman et al, 2006; Snik et al, 2005). However, many clinicians consider 45 dB as the upper limit for the application of this type of devices. Numerous reports have been published on active middle ear implants (AMEIs) in case of moderate MHL (Baumgartner et al, 2010; Beltrame et al, 2009; Bernardeschi et al, 2011; Colletti et al, 2013; Dumon et al, 2009; Martin et al, 2009; Schwab et al, 2012). Luers et al (2013) provided a recent overview of new coupling methods for an AMEI to the stapes structure and round window in case of conductive hearing loss or MHL. For severe MHL the outcome with active middle ear implants remains variable

(Verhaegen et al, 2012). Recently a new type of acoustic hearing implant (AHI) has been introduced for this type and degree of hearing loss: a direct acoustic cochlear implant (DACI). DACI couple directly to the inner ear, i.e. via the oval or round window or via a surgically created 'third-window'. As a result, pathological outer and middle ear structures of the ear are bypassed and the amplified signal is directly provided to the cochlea. Bernhard et al (2006) and Häusler et al (2008) first described a DACI called DACS. The successor of the DACS, the Codacs investigational device, has been applied in a first European multicenter clinical trial between 2009 and 2011, confirming the clinical efficacy and safety of the DACI in subjects with severe to profound MHL due to advanced otosclerosis (Lenarz et al, 2013).

Depending on the patient's individual situation, hearing loss due to otosclerosis can be treated with stapes surgery, HA, BCI or AMEI. HAs are usually very effective early in the course of the disease. However, when the conductive component increases, high power outputs are needed to compensate for the conductive component, which often leads to complications with feedback and distorted sound quality. In recent years, AMEIs were implanted in patients with moderate or severe MHL. Although the results in patients with moderate MHL are very promising, in patients with severe MHL they remain variable (Verhaegen et al, 2012). At a later stage of the disease, a stapes surgery may be required. Nevertheless after surgery, patients still have to wear a HA to compensate for the sensorineural hearing loss component. In more advanced otosclerosis, a cochlear implant (CI) is currently the only alternative treatment to a stapes surgery combined with postsurgery hearing aid amplification (Merkus et al, 2011). Other causes of profound MHL, which can be treated with DACI, are for example chronic otitis media with destruction of the ossicular chain and some degree of inner ear damage or tympanosclerosis.

A recent systematic review on the application of acoustic hearing implants for MHL concluded that most implants have favorable outcome, despite a high degree of variability in the results (Verhaert et al, 2013a). To accurately assess outcomes prospective and comparative studies are needed to compare speech perception in noise for different kinds of hearing implants and HAs and to collect long term data. The aim of the current study was to prospectively investigate the speech reception threshold (SRT) in noise for individuals with

MHL due to various etiologies using a DACI, compared to their performance preoperatively in the best-aided condition. In addition, postoperative functional results, subjective patient-reported outcome measures and adverse events are presented.

3.3 Material and methods

3.3.1 Population and study design

Twenty adult subjects were enrolled in this prospective study, running from January 2012 until February 2013 at five tertiary referral centers. Eight subjects were enrolled at the Hannover Medical School (Germany), 5 at the World Hearing Center (Poland), 3 subjects at the University Hospitals of Leuven, 2 at the University Hospital of Antwerp (both Belgium) and 2 at the University Hospital Insular De Gran Canaria (Spain). Table 3.1 gives an overview of the subjects' demographics. Nineteen of the 20 enrolled subjects were implanted with the Codacs investigational device (Cochlear Ltd., Sydney, Australia), which was described in detail by Lenarz et al (2013). One patient could not be implanted due to severe ossification of the cochlea, not identifiable on the CT scan preoperatively. This patient was excluded from the data analysis of the treatment outcomes. The average age at the date of implantation was 61 years (range 47-77 yrs). The study population consisted of 12 females and 8 males. All subjects had severe to profound MHL and met the eligibility criteria of the study (see Appendix A3). Eleven subjects were inconsistent users of a HA prior to surgery. Subjects not consistently wearing a HA preoperatively were fitted with a HA or BCI on a headband for the preoperative measurements. Care was taken to fit them with the most optimal hearing device according to their individual situation and hearing loss, e.g. a BCI in case of ear canal fibrosis. Non-HA users could not be fitted with a HA or BCI for a longer period of time due to logistical issues. However, most of the subjects had experience with hearing devices on the ipsilateral and/or contralateral ear (which facilitated the fitting procedure). On the contralateral ear, 9 subjects were fitted with a hearing aid, 1 subject had a CI (HiRes 90K, Advanced Bionics, Valencia, CA, USA), 1 subject was implanted with a Vibrant Soundbridge (VSB, MED-EL, Innsbruck, Austria), 1 subject was

wearing a DACS-PI (Phonak Acoustic Implants, Phonak AG, Stäfa, Switzerland) and 8 subjects did not use any amplification. The etiology of the hearing loss was otosclerosis for the majority of the enrolled subjects (n = 16, 80%), and tympanosclerosis, previous chronic otitis media, ear canal fibrosis and previous cholesteatoma each in 1 subject (5%). Nine of the 20 subjects (45%) had (several) previous surgery/surgeries in the implanted ear (stapedotomy, tympanoplasty, myringoplasty). The surgical technique to implant the direct acoustic cochlear implant was described by Lenarz et al (2013).

Each subject served as his/her own control in this prospective single-subject repeated-measures study design. Given the paired setup of the study, the measurements done prior to implantation with the DACI and at 3 months after the initial activation of the DACI were compared pairwise using the paired Student's t-test (parametric test) or the Wilcoxon matched-pairs signed-rank test (nonparametric test). The normality of the data distributions was checked with a one-sample Kolmogorov-Smirnov test. Only complete datasets were included for statistical analysis. In case of the presence of outliers and/or low numbers of complete pairs and/or no normal data distribution, nonparametric testing was used. Statistical analysis was performed with PASW 20.0 (SPSS Software®, SPSS Inc, Chicago, IL, USA). Throughout the entire statistical analysis, a significance level of 5% was adopted. A power calculation was done prior to the study to define the required number of subjects. All patients gave their written informed consent before being enrolled in the clinical trial. This study was approved by the ethical committee of each center and the competent authority of each country involved in the trial. The principles outlined in the Declaration of Helsinki (2008) were followed.

Table 3.1 Subject's demographics.

Subject	Gender	Age years	Implanted ear	Duration use of current HA in implanted ear	Preop. Aided measurements	Previous operations implanted ear	Previous operations contralateral ear	Reason for conductive hearing loss
1	F	71	right	1 to 5 years	own HA	tympanoplasty (1985 and 1995)	Vibrant Soundbridge (2010)	ear canal fibrosis
2	F	75	right	1 to 5 years	own HA	no	no	otosclerosis
3	M	51	right	currently no HA	Baha Intenso	stapedotomy (2000 and 2009) tympanoscopy (2010)	no	otosclerosis
4	F	69	left	1 to 5 years	own HA	stapedectomy (1977) / revision stapedectomy (1979)	stapedotomy (1996) / CI (2008)	otosclerosis
5	F	62	right	currently no HA	Baha Cordelle	no	stapedectomy (1979)	otosclerosis
6	F	70	right	5 to 10 years	own HA	no	stapedectomy (1978) / revision stapedectomy (1983)	otosclerosis
7	F	55	right	currently no HA	Baha Cordelle	mastoidectomy (2007 and 2011)	no	chronic otitis media
8	F	63	left	5 to 10 years	own HA	no	atticotomy and revision tympanoplasty (1999) / implantation DACS-PI (2011)	otosclerosis
9	F	61	left	5 to 10 years	own HA	no	no	otosclerosis
10	M	77	right	15 to 20 years	own HA	no	no	otosclerosis
11	M	49	right	currently no HA	Baha Intenso	no	no	otosclerosis
12	F	58	left	currently no HA	Baha Cordelle	no	cholesteatoma (2x in 2010) tympanoplasty (2010 -2011)	tympanosclerosis
13	M	59	left	currently no HA	Baha Cordelle	tympanoplasty cholesteatoma) (2002)	surgery for cholesteatoma treatment (1991)	cholesteatoma
14	M	53	left	currently no HA	Phonak Naida V	stapedotomy (2002) / re-stapedotomy and myringoplasty (2011) / revision after re-stapedotomy (2011)	no	otosclerosis
15	F	71	right	currently no HA	Phonak Naida V	no	no	otosclerosis
16	M	43	left	currently no HA	Phonak Naida V	no	no	otosclerosis
17	M	70	right	15 to 20 years	Phonak Naida V	stapedotomy (2008)	no	otosclerosis
18	M	48	left	5 to 10 years	own HA	no	no	otosclerosis
19	F	76	left	currently no HA	Baha BP 110	myringoplasty (1982)	no	otosclerosis
20	F	45	left ear not implanted	currently no HA	Baha BP 110	stapedectomy (2011)	stapedectomy (2006)	otosclerosis

3.3.2 Audiometric Testing

Pre- and postoperatively, all subjects underwent comprehensive audiological and medical evaluations. Audiological testing consisted of air conduction (AC, 0.125-8 kHz) and bone conduction (BC, 0.25-4 kHz) audiometry. Sound field measurements were performed with warble tones ranging from 0.125 to 8 kHz (including half-octave bands) with the speaker positioned at 0° azimuth in unaided and aided conditions with the contralateral ear plugged and masked. All subjects were measured in their best-aided condition preoperatively, using their own HA (40%), a clinical trial/loan HA (20%) or a BCI (Baha Cordelle, Intenso or BP110) on a headband (40%), the latter two for acute testing. The DACI was activated 6 to 8 weeks after surgery. Preoperatively, and subsequently postoperatively at time of activation, 1 and 3 months after activation, speech reception tests were performed in aided condition with the contralateral ear plugged and masked if required. Speech audiometry tests using standardized Dutch (NVA monosyllables), German (Freiburger monosyllables), Polish (Pruszewicz monosyllables) and Spanish (bisyllabic) words were performed to assess the patients' word recognition scores (WRS) in quiet at 50, 65 and 80 dB SPL. To evaluate the SRT in noise adaptive sentence tests in noise were used with a noise level fixed at 65 dB SPL (Belgium: LIST sentences; Germany: OLSA; Poland: sentence matrix test; Spain: Spanish HINT sentences) at 0° azimuth with speech and noise both coming from the front (S_0N_0), 3 months after activation. The SRT is defined as the signal-to-noise ratio (SNR), at which 50% of the words in a sentence are correctly repeated. The test setup was consistent in all centers. At each follow-up visit, the sound processor was adjusted with dedicated fitting software according to the subjects' hearing loss and comfort.

3.3.3 Patient-reported outcome measures

Subjects responded to the Abbreviated Profile of Hearing Aid Benefit (APHAB) and Health Utilities Index (HUI®) questionnaires for both the preoperative (aided or unaided) and the postoperative condition (3 months after activation) to assess the patients' satisfaction with the system. Each subject reported the amount of difficulty experienced with communication in various everyday situations. The APHAB produces scores of four subscales: ease of

communication (EC), reverberation (RV), background noise (BN) and aversiveness (AV) (Cox & Alexander, 1995). Higher scores reflect more communication problems. A difference of 22% or more in any of the 3 subscales EC, BN and RV or of 31% or more in the AV subscale or a difference of 10% in the global score is considered a clinically relevant difference as reported by the developers. The HUI is a generic, preference-scored, comprehensive system for measuring the overall health status and the health-related quality of life and can be used to calculate hearing utility scores. The HUI used in this study was a self-administered 15-item questionnaire.

3.4 Results

As mentioned above, all preoperative aided data are measured in the subject's best-aided condition i.e. with HA or BCI on a headband. The APHAB and HUI data reflects the patient's pre-operative binaural condition i.e. binaurally unaided, monaurally aided or bilaterally aided. The postoperative aided data is measured 3 months after activation of the DACI, i.e. approximately 5 months after surgery in the subject's everyday DACI-aided condition. All but 1 subject are daily DACI-users.

3.4.1 Audiometric results

Speech reception in noise The average and individual SRTs in noise for 19 subjects for the preoperative and postoperative aided condition were assessed and are shown in Figure 3.1. Five subjects could not perform the test preoperatively, including 2 who were not able to perform the test postoperatively. For these subjects, the easiest possible test condition, an SRT of +20 dB SNR, was determined as their SRT in noise score. Sixteen subjects (84%) had better postoperative results compared to the preoperative condition (light area in Figure 3.1). An improvement of more than 2 dB SNR (statistically significant and clinically relevant difference, higher than the known test-retest variability of the used adaptive sentence tests in noise) was measured in 14 (74%) of these subjects. In 2 subjects (11%) no improvement concerning speech perception in noise was found; they were not able to perform the test either pre- or postoperatively. One subject showed a slightly poorer result

postoperatively while not statistically significant (difference of -0.8 dB SNR, dark area in Figure 3.1).

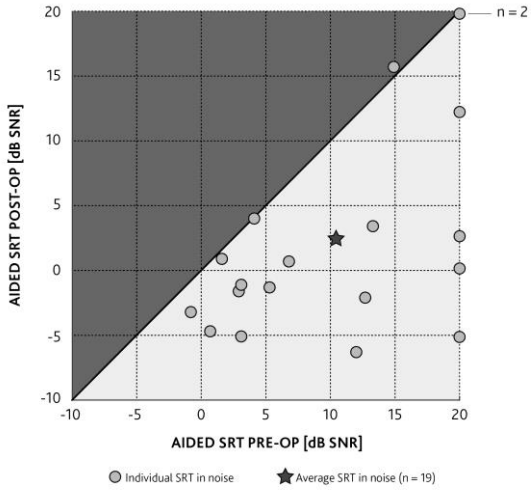

Figure 3.1 Individual and average SRTs in noise for 19 subjects tested preoperatively with HA or BCI and 3 months after activation with DACI. Star shows average SRT in noise of 2.6 dB SNR (SD 8.3 dB).

For the group of 19 subjects, a mean postoperative aided SRT of 2.6 dB SNR (standard deviation (SD) = 8.3 dB) was noted. This represents a statistically significant mean improvement of 7.9 dB (SD = 7.6 dB) compared to the preoperative aided condition for the study cohort ($p < 0.001$).

AC and BC, sound field thresholds Figure 3.2 and Figure 3.3 show the individual and mean preoperative and postoperative pure tone threshold (pure-tone average, PTA, average of hearing thresholds at 0.5, 1, 2 and 3 or 4 kHz) for AC and BC for the 19 implanted subjects, respectively. Preoperatively, the AC and BC PTA were 92 dB HL (SD= 1.5 dB) and 57.8 dB HL (SD= 5.2 dB), respectively, with a mean air-bone gap of 35 dB (SD= 6.9 dB), indicating a severe to profound MHL for the group. The postoperative AC and BC PTA were 95.4 dB HL (SD= 4.1 dB) and 57.2 dB HL (SD= 7.6 dB), respectively. On average, the postoperative AC thresholds did not change significantly compared to the preoperative condition ($p > 0.05$), as can be seen by the triangle lying close to the straight line in Figure 3.2.

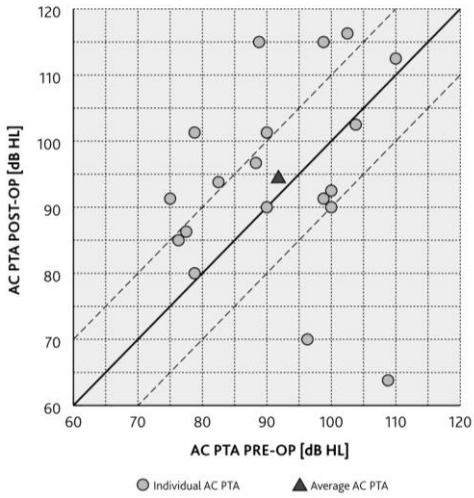

Figure 3.2 Individual and mean (n = 19) pre- and postoperative AC thresholds. Dotted lines show clinically significant mean PTA shift of 10 dB.

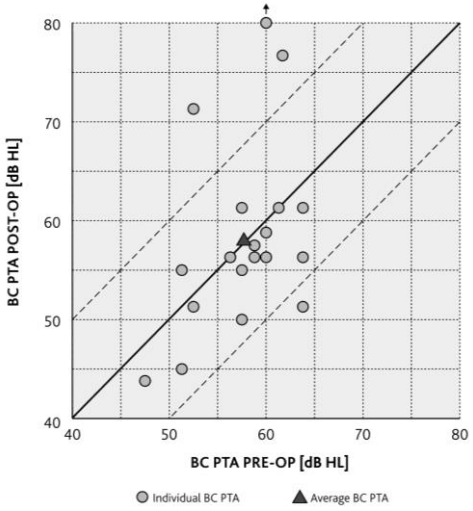

Figure 3.3 Individual and mean (n = 19) pre- and postoperative BC thresholds. Dotted lines show clinically significant mean PTA shift of 10 dB.

Twelve subjects (63%) had poorer AC thresholds after surgery, while in 6 subjects (32%) the AC thresholds improved. In 1 subject (5%), thresholds did not

change. On average, the BC thresholds did not change significantly compared to the preoperative condition ($p > 0.05$), except at 0.750 kHz, where there was a significant improvement ($p = 0.009$). The preservation of the preoperative BC thresholds is indicated by the triangle lying on the straight line in Figure 3.3. In 1 of the subjects (5%), a statistically significant improvement of the BC thresholds was measured. Three subjects (16%) had a clinically significant (defined as a mean PTA shift > 10 dB) decrement in hearing threshold after surgery. In 1 of those subjects, BC thresholds could not be measured any more after surgery (marked by an arrow on the postoperative PTA of 80 dB HL). This subject had a tympanosclerotic stapes fixation with additional intracochlear ossification, encountered during stapedotomy. The BC thresholds of this subject did not recover and the event was reported as a serious adverse event to the competent authorities.

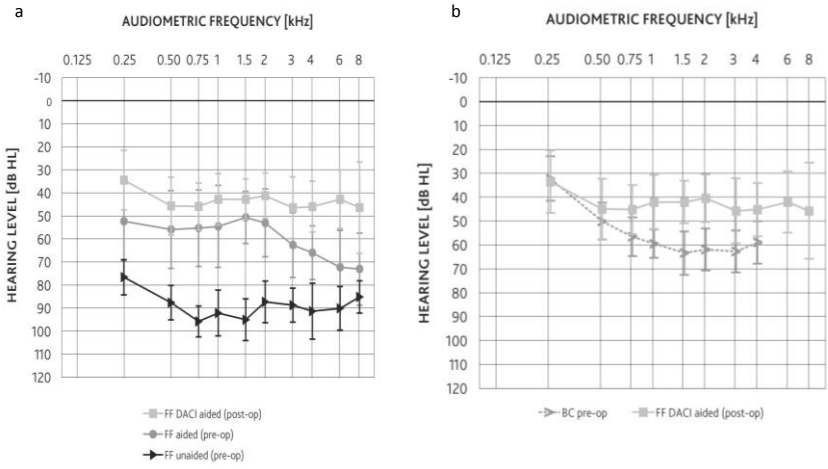

Figure 3.4 Mean (n = 19) pre- and post-operative unaided and aided free field (FF) thresholds (**a**) and BC thresholds and postoperative DACI-aided sound field thresholds (**b**). Error bars show SDs.

Figure 3.4a depicts the mean unaided and aided sound field thresholds for 19 subjects. The mean preoperative unaided and hearing aid/BCI-aided sound field thresholds were 88.9 dB HL (SD= 5.5 dB) and 59.3 dB HL (SD= 8.4 dB), respectively. The mean postoperative DACI- aided sound field threshold was 43 dB HL (SD= 3.7 dB). Thus, the mean improvement by the hearing aid/BCI was

29.6 dB whereas the mean improvement by the DACI was 45.9 dB. A significant improvement in favor of the DACI ($p < 0.05$) compared to the preoperative unaided and aided thresholds was observed over all frequencies (except for 8 kHz). The mean overclosure of the air-bone gap defined as the difference between the postoperative DACI-aided sound field thresholds and the preoperative BC thresholds, was 15.6 dB as shown in Figure 3.4b.

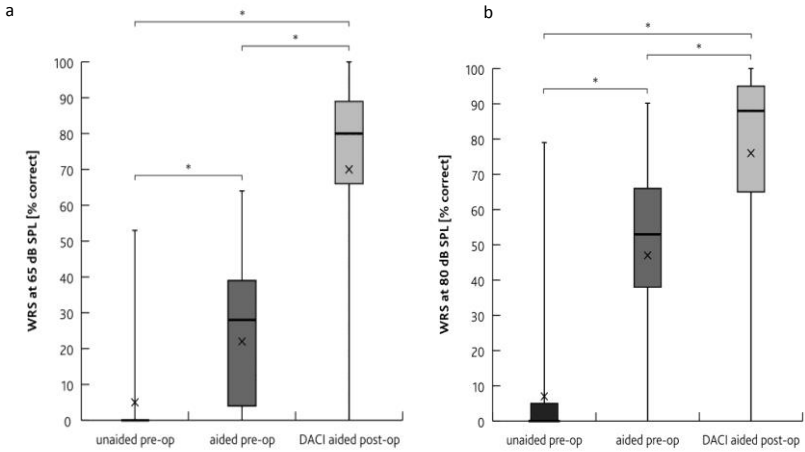

Figure 3.5 Mean (n = 19) WRS (% correct) for presentation levels of 65 dB SPL (**a**) and 80 dB SPL (**b**) for the preoperative unaided and aided condition and for the postoperative DACI-aided condition 3 months after activation. Lines shows median, crosses mean and error bars show SDs. *$p < 0.005$.

Speech Reception in quiet Speech reception in quiet was evaluated by measuring the WRS using recorded speech at input levels of 50, 65 and 80 dB SPL. The WRS were measured preoperatively unaided and hearing aid/BCI aided and postoperatively aided with the DACI. The WRS improved significantly by 31% (SD= 31, $p = 0.003$), 65% (SD = 34, $p < 0.001$) and 69% (SD = 35, $p < 0.001$) at 50, 65 and 80 dB SPL, respectively, compared to the preoperative unaided condition and by 26% (SD = 32, $p = 0.004$), 48% (SD = 37, $p < 0.001$) and 29% (SD = 37, $p < 0.001$) at 50, 65 and 80 dB SPL, respectively, compared to the preoperative aided condition. Figure 3.5 demonstrates the unaided and aided WRS at 65 dB SPL (a) and 80 dB SPL (b), respectively.

3.4.1 Subject's satisfaction

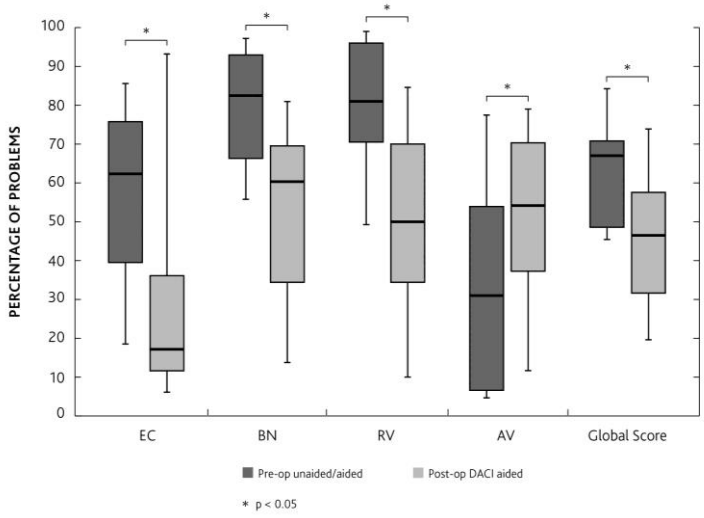

Figure 3.6 Mean (n = 19) difficulty in hearing shown for the four subscales and the global score of the APHAB. Error bars show SD. *$p < 0.05$.

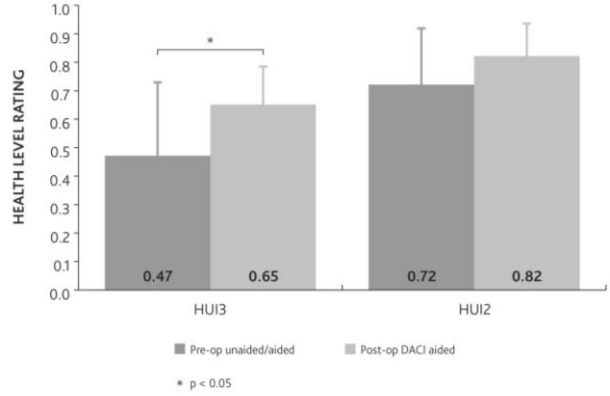

Figure 3.7 Mean (n = 19) HUI index (HUI 3 and 2) of the HUI questionnaire. Error bars show SD. * $p < 0.05$.

APHAB Score results Figure 3.6 provides a summary of the APHAB subscales and global scores for the 19 subjects with respect to their preoperative (i.e. unaided or HA-aided) and their postoperative DACI-aided

condition. Three subscales (EC, BN and RV) improved significantly by 28% (p < 0.001), 27% (p < 0.001) and 28% (p < 0.001), respectively, after implantation with the DACI. The AV subscale worsened significantly by 16% (p = 0.02), which is clinically not significant. Overall a global benefit in hearing ability was recorded at 16% (p < 0.001) for the group, which is both clinically and statistically significant.

HUI overall utility score Figure 3.7 shows the average HUI2 and HUI3 scores for 19 subjects for their preoperative daily listening condition (i.e. unaided or HA-aided) and postoperative in the DACI-aided condition. Improvements for scores on the HUI3 by 0.18 (p = 0.009) were significant while scores improved on the HUI2 but were not significantly better (0.09, p = 0.064). A difference of 0.03 in the overall HUI score is considered clinically relevant (Drummond, 2001). The average improvement for the HUI3 and HUI2 combined scores is clinically significant. The majority, 79% of the subjects (15/19) have a clinically relevant improvement of more than 0.03 in their HUI3 score and just over half, 58% (11/19), of more than 0.03 in their HUI2 score.

3.4.2 Safety

The DACI could be implanted in 19 of the 20 enrolled subjects. One subject was not implanted with the DACI due to severe ossification in the cochlea, which could not be identified on the CT scan pre-operatively. The surgeon decided not to implant the DACI to minimize the risk of sensorineural deafness. During the trial 4 serious adverse events and 7 adverse events were reported. None of the serious adverse events were rated as device-related; two serious adverse events (retro-auricular abscess and increased hearing loss) were rated as procedure-related. The remaining two serious adverse events were unrelated to the device or the procedure. One adverse event was rated as device- and procedure-related (skin irritation in the fold behind the ear) and four adverse events were rated as possibly device-related (tinnitus, deterioration of bone conduction thresholds, vertigo, vertigo and instability and otitis media) with a potential procedure relationship for 4 of them. All but 2 events are resolved. One subject still had mild vertigo at the end of the study. Another subject with preoperative profound MHL (and a moderately severe sensorineural

component) due to a tympanosclerotic stapes fixation showed an additional hearing loss on nearly all frequencies after surgery as stated above. Stapedotomy in this subject was laborious due to intracochlear ossification. The subject experienced no WRS improvement and no longer wears the DACI device. Up to the time of writing this manuscript, no technical device failures were reported.

3.5 Discussion

3.5.1 Speech in noise and quiet

In the current study, the SRT in noise improved by 2 dB or more in 74% of the subjects and the mean improvement was 7.9 dB. Preoperatively, little hearing benefit in quiet and noise was achieved with previous middle ear surgery, best fitted HA or BCI, as shown by poor speech test results preoperatively (mean aided SRT in noise of 10.5 dB SNR, mean aided WRS at 65 dB SPL of 24%). Some subjects were not able to wear a hearing aid preoperatively due to external ear canal problems. For patients with BC thresholds up to 45-50 dB HL, a BCI can be considered as an alternative treatment, and preferably the more powerful body-worn Baha Cordelle (Bosman et al, 2006; Snik et al, 2005). However, our study cohort displayed mean preoperative BC thresholds of 57.8 dB HL which lies above the upper indication limit, hence adequate amplification with the body-worn BCI was questionable. In a descriptive study of Verhaegen et al (2009) on 5 subjects with profound MHL, outcomes with a BCI (Baha Cordelle) were compared to those with a CI. They concluded, that if the speech perception score (phoneme score) at 65 dB SPL in quiet was less than 42% with the tested BCI preoperatively, a CI is a valuable option. In the current study, 2 out of 4 subjects that were tested preoperatively with a Baha Cordelle (on a headband), showed a mean score (word score) of 35% in quiet at 65 dB SPL, i.e. a CI would be recommended for them following the criteria of Verhaegen et al (2009). However, better postoperative word scores would be expected after osseo-integration of the percutaneous BCI compared to the transcutaneous use in this study (Heywood et al, 2011). But it is also known that for severe to profound high frequency loss this disparity is less relevant. Also, Snapp et al

(2013) showed that there was no significant difference between preoperative speech in noise testing with the Baha Cordelle headband stimulator and the postoperative results with the implanted device in their study. Postoperatively, those 4 subjects had a mean score of 68% with the DACI. In general, most patients prefer an ear level device to a body-worn device, and feedback can be an issue with the body-worn BCI. In the current study it was shown that subjects with a mean BC threshold of 57.8 dB SPL could reach a mean WRS score of 70% at 65 dB SPL with the DACI.

By implanting the subjects with a DACI, a CI surgery can be avoided and the cochlear reserve can be maintained and further utilized. As significant improvement in performance was observed for the group at the 3-month follow-up, one may hypothesize DACI patients adapt to the sound stimulation readily after implant fitting and it is expected that rehabilitation efforts and time will be considerably less than with a CI. Residual hearing can be preserved in CI surgery when using soft surgical techniques even with more conventional electrodes up to 50% (Fraysse et al, 2006). However the question still remains to what extent this residual hearing in conventional CI candidates is serviceable. Recent studies with the latest 'soft' electrodes, show higher rates of hearing preservation and aidable low frequency hearing in selected subjects (Büchner et al, 2009; Skarzynski et al, 2012). In the current study, 1 subject with profound MHL showed significant additional hearing loss at implantation. The subject had a tympanosclerotic stapes fixation. Studying the literature, one can notice that tympanosclerosis patients can benefit from stapes surgery with no major risk to the cochlea if careful patient selection and surgical technique is applied (Vincent et al, 2002). However, its surgical treatment remains a great challenge and surgeons should carefully select patients with this indication for DACI surgery. Other adverse events described above were mainly transient and are well known risks associated with stapes and implant surgery. In a systematic review by Verhaert et al (2013) complications from acoustic hearing implants were listed. Main complications were FMT displacements and wound healing problems. Additional inner ear damage was described in a few cases.

Although the used sentence in noise tests were developed for severely impaired persons, and measuring the SRT has the advantage to avoid ceiling effects (van Wieringen & Wouters, 2008), 5 subjects in the current study could not perform

the test preoperatively. In their study, the authors also found that 2 out of 16 CI subjects found the task too difficult.

Finally it should be noted that while the ossicular chain was disrupted during the surgical procedure to implant the DACI in the current study, no significant change in AC thresholds was measured for the study cohort. This may be explained by the presence of a profound hearing loss with complete stapes fixation and no middle ear amplification before implantation.

3.5.2 Study quality

Comparing the current results with other DACI or AMEI, such as the VSB or Carina/MET (Otologics & Cochlear™, Boulder, Colo., USA), remains difficult due to different study setups reported, different speech material and the lack of comparative data on preoperative use of HA or BCI (Verhaert et al, 2013a). As suggested in this review, the current study was designed as a multicenter, prospective study, using comparable speech material in four languages, enhancing the possibility to compare data. Very few studies, always through retrospective data collection, have published speech in noise results comparing the use of AHI to preoperative hearing aid scores. When comparing the VSB aided condition to an aided or unaided preoperative condition, reports show a variable improvement of 2.8 to 5 dB SNR (Beltrame et al, 2009; Böheim et al, 2012; Rajan et al, 2011). Remarkably, with the current DACI, aided sound field thresholds show amplification on all frequencies i.e. an overclosure of the air-bone gap, whereas it is known that other AHI, such as the VSB, show less amplification on the lower frequencies and are mostly not able to close the air-bone gap in the low frequencies. The current results concur with previous results on the DACS (Häusler et al, 2008), reporting a significant improvement of speech understanding in noise in 2 subjects, compared to the unaided condition. A first clinical trial with the Codacs investigational device implanted in 15 subjects showed comparable results with the results reported here (Lenarz et al, 2013). In a subgroup of 11 out of 15 subjects aided preoperative scores were available, showing a statistically significant improvement in the DACI condition compared to the hearing aid condition. The postoperative aided SRT in noise, measured in 12 subjects, was 0.3 dB. WRS at 65 and 80 dB SPL improved significantly by 35.5% and 25.7%, respectively, compared to the

preoperative aided condition. In contrast with the current study, no systematic comparison to the preoperative aided condition with hearing aid or BCI, allowing for direct comparison between different solutions for hearing rehabilitation, was made in that study. Also different etiologies for MHL were treated in the current study whereas in the previous study MHL only due to otosclerosis was included.

3.5.3 Alternatives

A recent study determined the effectiveness of primary stapes surgery in patients with profound hearing loss due to far-advanced otosclerosis (Lachance et al, 2012). On average, the sentence recognition score after surgery with well fitted hearing aids improved by 54.4% compared to the preoperative aided condition with well-fitted HAs. However, a wide variability in outcomes from 0% to 93% existed. After stapes surgery, 87% of patients were no longer CI candidates.

For conductive hearing loss and moderate MHL, newer coupling methods to the stapes with titanium couplers, so far described in mobile footplate cases, show more stable results than previous reports (Luers et al, 2013). The authors expect that by using titanium couplers, described by Hüttenbrink et al (2011) as a clip vibroplasty, surgeries with AMEI will be performed in a more standardized manner, possibly diminishing the current variable functional hearing gain after VSB implantation (Luers et al, 2013). In several studies, stapes fixation was encountered during VSB implantation without safe access to the round window, mainly due to congenital middle ear malformation (Beleites et al, 2011; Verhaert et al, 2011). Some authors, mostly for safety, coupled the floating mass transducer to the fixed stapes, as that procedure follows the normal auditory pathway, keeping the round window as a pressure outlet, achieving however suboptimal amplification. Also Devèze et al (2010) experimentally demonstrated a mean attenuation of 25 to 40 dB with a fixed stapes compared to a mobile stapes. Their study explains the suboptimal result, as the floating mass transducer cannot provide enough power to overcome the damping effect, mainly for the low frequencies. These reports demonstrate the need for direct acoustic coupling in pathologies other than otosclerosis. It is assumed that direct acoustic cochlear stimulation by DACI, overcomes the nonlinearities

caused by the stapes footplate fixation, possibly leading to a more natural hearing compared to overcoming the air-bone gap by acoustical amplification. Another potential solution is coupling the VSB directly with a TORP through a stapedotomy (Schwab et al, 2012). More and long-term results are needed for this application.

Some studies have mentioned a window of opportunity for CI in otosclerosis (Merkus et al, 2011; Ramsden et al, 2007; Rotteveel et al, 2004). Although this will be true in cases of extensive cochlear involvement seen on high-resolution CT, evidence is lacking regarding the length of this time window. Even after a successful cochlear implantation, the speech and hearing rehabilitation in subjects with otosclerosis due to progressive otosclerotic changes in the cochlea can affect the performance of the implant (Toung et al, 2004). One could also hypothesize that providing several years of hearing rehabilitation with a DACI could mean a more rapid revalidation, as more spiral ganglion neurons are preserved due to a more adequate acoustic stimulation pattern. Although this sounds logical, proof is still needed. But in case of severe otosclerotic progression, the option for CI remains open in DACI subjects.

There is a certain degree of variability in the results of the current study. This variability in success rates is also reported in stapedotomy for far-advanced otosclerosis. Outcome prediction remains a problem. The cochlear reserve of the ear to be implanted is difficult to determine due to bilateral mixed hearing loss. Several methods for outcome prediction are under discussion and will be evaluated in future studies.

3.6 Conclusion

The data presented here show that individuals with severe to profound MHL due to various etiologies and previous middle ear surgeries can substantially benefit from direct acoustic cochlear stimulation. The DACI used in this study provides a statistically significant mean improvement of the speech performance in quiet and in noise compared to the preoperative aided condition. It improves the ability of patients to communicate in everyday situations and their quality of life. No unanticipated device-related adverse

event occurred. As a consequence, DACI treatment can be considered a safe hearing treatment with acceptably low risks that are outweighed by the hearing benefits provided to the patients. Careful selection of patients, with a complete evaluation of the inner and middle ear imaging, is required by the implanting team to confirm suitability for surgery.

3.7 Acknowledgments

The study protocol was designed in collaboration with the five mentioned centers and Cochlear. The authors are grateful to K. De Voecht for her generous contributions to this work. N. Verhaert was partially supported by the Research Foundation Flanders.

Chapter 4
Transient and steady state auditory responses with direct acoustic cochlear stimulation[6]

4.1 Abstract

Objective: Direct Acoustic Cochlear Implants (DACIs) directly stimulate the cochlear fluid of the inner ear by means of a stapes piston driven by an actuator, and show encouraging speech understanding in noise results for patients with severe-to-profound mixed hearing loss. Auditory evoked potentials (AEPs) recorded in such patients would allow for the objective evaluation of the aided auditory pathway. The aim of this study was (1) to develop a stimulation setup for EEG recordings in subjects with Cochlear DACIs, (2) to show the feasibility of recording auditory brainstem responses (ABRs) and auditory steady state responses (ASSRs) and (3) to analyze the relation between electrophysiological thresholds derived from these responses and behavioral thresholds. **Design:** For the 3 subjects implanted during a phase Ib clinical study in our center, ABRs and 40 and 80 Hz ASSRs were recorded with a straightforward acoustic stimulation setup and a newly developed direct stimulation setup. Click trains with rates around 40 Hz and around 90 Hz were used as stimuli. By comparing amplitude growth function and phase delay in the same stimulus range, validity of the responses was confirmed. **Results:** With the acoustic stimulation setup, stimulation artifacts made it impossible to analyze responses. With the direct stimulation setup, stimulation artifacts could be removed completely and responses could be successfully recorded in a non-

[6] The content of this chapter has been submitted for publication to *Ear and Hearing* as Verhaert N. and Hofmann M., Wouters J. "Transient and steady state auditory responses with direct acoustic cochlear stimulation."

invasive manner in all subjects. Response properties such as ABR peak V latencies and ASSR apparent latencies were similar to those for acoustic stimulation, with apparent latencies of 39.9 and 24.7 ms for 40 and 90 Hz, respectively. Electrophysiological thresholds could be objectively determined from the ABRs and ASSRs. In the 40 Hz range, the mean difference between electrophysiological ASSR thresholds and behavioral ones was 12 dB. **Conclusion:** The results show that AEP measurements with the developed direct stimulation setup are feasible and meaningful and could potentially be used to provide intra-operative feedback about the coupling of the actuator to the inner ear.

4.2 Introduction

For patients with severe to profound mixed hearing loss (MHL), several different treatment options are available. As some cochlear reserve remains, acoustical stimulation, utilizing the human cochlear function, can improve audiological results in difficult listening conditions (Büchner et al, 2009). Nevertheless, due to the severity of hearing loss, conventional hearing aids and less powerful acoustic hearing implants will only have limited benefit (Verhaert et al, 2013a; Zwartenkot et al, 2014). Electrical stimulation of the cochlea through cochlear implants (CIs) is another well-established therapy but requires longer rehabilitation, could cause fitting problems such as facial nerve stimulation, lacks speech's fine structure coding and shows limited F_0 information transmission (Toung et al, 2004).

Recently, a powerful acoustic hearing implant for direct acoustic cochlear stimulation was developed and showed encouraging results for speech understanding in noise, being an indicator for real-life communication, for subjects with severe to profound MHL (Busch et al. 2013; Lenarz et al. 2013; Lenarz and Verhaert et al. 2014). Subjects with bone conduction thresholds classifying them as CI candidates were able to achieve remarkable improvements in speech understanding in noise with direct acoustic stimulation. Additionally, much faster speech and hearing rehabilitation compared to the period typically observed after cochlear implantation was noted. In this implant system, an actuator causes mechanical movement of a

rod coupled to the inner ear fluid at the level of the oval window. By doing so, the direct acoustic cochlear implant (DACI) provides the amplified signal directly to the cochlea, through an acoustical pathway.

At this stage of development, an important challenge for DACIs is the assessment and fitting of this device to the needs of the individual patient. For established hearing implants such as CIs, several objective electrophysiological measures are available. Electrically evoked auditory potentials can be recorded from within the cochlea (Brown et al, 1990). Auditory brainstem responses (ABRs), regularly used for threshold determination in infants, have been determined experimentally during stapedotomy surgery (Stapells & Oates, 1997; Hsu, 2010). Initially proposed for clinical hearing testing (Galambos et al, 1981), auditory steady-state responses (ASSRs) can also be used in CI subjects (Ménard et al, 2004; Hofmann & Wouters, 2010, 2012). Although direct cochlear acoustical stimulation was proven to be clinically effective and safe with approval for clinical use in Europe, the availability of such measures for DACIs is important for the objective evaluation of large parts of the auditory pathway both during (intra-) and after implantation (postoperatively). As the number of implantations will grow significantly, early research in this field is urgently needed, also providing the necessary tools to objectively evaluate the outcome of new applications, e.g. in case of alternative DACI coupling to the inner ear.

The objectives of this study were (1) to develop objective electrophysiological measures for direct acoustic cochlear stimulation in humans, both in the time domain (ABRs) and frequency domain (ASSRs), and (2) to evaluate the ability of such responses to assist in future intra-operative testing and the device's fitting process.

Table 4.1 Overview of the tested subjects. Sex: M male, F female; age: at the time of testing (in years); PTA: unaided average pure tone audiometry threshold at 0.5, 1, 2 and 3 kHz, AC air conduction, BC bone conduction.

Subject	Sex	Age	PTA (AC/BC) in dB HL	Side	Etiology
S1	F	62	96/58	left	otosclerosis
S2	M	78	117/64	right	otosclerosis
S3	M	50	111/66	right	otosclerosis

4.3 Methods

4.3.1 Subjects and device

So far, only a limited number of subjects in a few countries were implanted. The implantations occurred during a multicenter clinical study (Lenarz and Verhaert et al. 2014). Three subjects with severe to profound MHL were implanted at the University Hospitals Leuven and all of them took part in the experiments (Table 4.1). The subjects suffered from advanced otosclerosis and underwent an implantation with a Cochlear Codacs DACI (Bernhard et al, 2006). Clinical and surgical information are described in detail in Lenarz et al. (2013). All the experiments on subjects were performed at least four months after activation of the DACI device. The experiments were approved by the Medical Ethics Committee of the UZ Leuven/KU Leuven (approval number B322201112184). The protocol had been assigned with a NCT01780025 ClinicalTrials.gov ID. The subjects took part voluntarily and gave their written informed consent.

The Codacs DACI system consists of an external speech processor and an internal implant connected by a wireless radio-frequency (RF) transmission link that provides both power and a bidirectional communication link. The incoming acoustic signal is received by the speech processor, sampled at a rate of 19607 Hz and preprocessed. Each individual sample is then converted to an RF frame and transmitted to the implant along a 5 MHz RF link (Zeng et al, 2008). The RF frames are decoded in the implant and used to drive an electro-magnetic actuator in the middle ear. The actuator in turn is connected to a conventional stapes prosthesis coupled to the perilymph of the inner ear.

4.3.2 Stimulation and recording setup

The stimulation and recording setup are shown in Figure 4.1. The experiments are controlled by a measurement laptop equipped with the RBA measurement software platform developed in our lab (Hofmann & Wouters, 2012). RBA handled both the generation of the stimuli and the recording of the evoked responses. Two different methods for the generation and transmission of the auditory stimuli were evaluated.

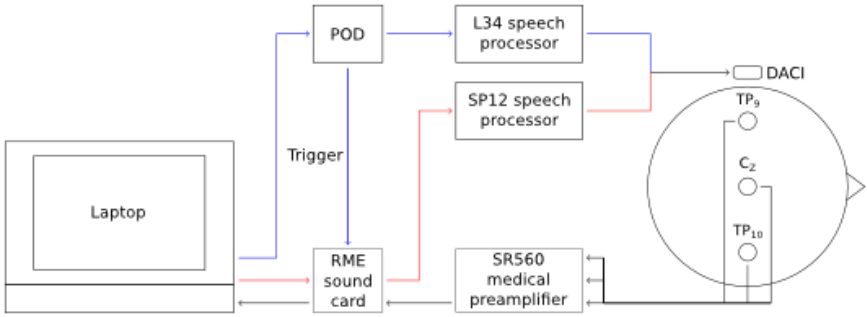

Figure 4.1 Stimulation and recording setup. POD: programming device. Line colors show connections for different stimulation setups: red – analog stimulation, blue – direct stimulation.

For analog stimulation, the stimuli generated by RBA at a sample rate of 32 kHz were provided to an external RME Hammerfall DSP Multiface II sound card, which was connected via the personal audio cable accessory to a Cochlear Freedom™ speech processor. The speech processor was equipped with a special pass-through firmware that did not modify the acoustic signal from the audio cable. The optional equalizer of the firmware was disabled. For direct stimulation, the stimuli were generated at the frame rate of the DACI of 19607 Hz. The digital stimuli were directly sent to a programming device (POD) connected to a Cochlear L34 research speech processor. For both methods, the clinical processor of the subjects was not used. Whereas the analog stimulation setup was more or less readily available, the direct stimulation mode needed to be developed. By analyzing and comparing both methods, the most optimal stimulation method for AEP recording was obtained.

For recording, surface electrodes were placed on the head of the patients in accordance with the international 10-20 system (Malmivuo & Plonsey, 1995) at conventional ASSR positions (Johnson & Brown, 2005). The reference (negative) electrode was placed on the ipsilateral mastoid (TP_9 or TP_{10}) relative to the side of the implanted DACI. The active (positive) electrode was placed on the vertex (C_Z), and the ground electrode was placed on the contralateral mastoid (TP_9 or TP_{10}). The electrode-skin contact was prepared by scrubbing and cleaning, with resulting electrode impedances of 5 kΩ or less as verified with a General Devices EIM-107 Prep-Check Plus EEG electrode impedance meter. The electrodes were connected to a Stanford Research Systems SR560 medical

preamplifier with a variable gain of 20000 to 50000. The internal linear band pass filter (6 dB/octave attenuation outside the pass band) of the amplifier was set to 0.3 Hz to 30 kHz. The amplified signal was recorded by the RME sound card and saved on the measurement laptop. Recording occurred at a sample rate of 32 kHz with 24 bit resolution at about 10 V_{PP}, resulting in a least-significant bit (LSB) of 0.02 nV at an amplification of 50000.

For analog stimulation, stimulation and recording were inherently synchronized as both were done with the same RME. The latency between stimulation and recording because of the processing delay in the personal audio cable was determined by the position of the stimulus artifacts (see below). For direct stimulation, trigger pulses generated by the POD for each stimulus were recorded by the RME alongside the EEG.

During the measurements, the subjects were either sitting in a comfortable chair or lying on a couch and instructed to move as little as possible. They watched a silent subtitled movie to keep them awake.

4.3.3 Stimulus construction and verification

For all experiments, the stimulus intensity was expressed in dBpeFS, i.e. as the level of a sinusoid with the same peak amplitude as the stimulus clicks, relative to the level of a maximum-amplitude sinusoid generated with direct stimulation. For analog stimulation, monophasic alternating (condensation – rarefaction) clicks with a click width of 100, 200 and 300 µs were generated by the RME. For direct stimulation, monophasic alternating clicks with a click width of 102, 204 and 306 µs, corresponding to 2, 4 and 6 RF frames, respectively, were used.

Correctness of stimulation was verified in a three-step procedure. In the first step, the stimulation patterns were validated with an oscilloscope connected to a DACI implant-in-a-box (IIB). The scope showed the RF signal from the coil obtained by inductive coupling, the actual sample values decoded from the RF frames and the output of the IIB to the actuator (Figure 4.2). In this figure an example of direct stimulation was given, using clicks with alternating polarity. The output signal was also provided to a pair of headphones. For direct stimulation, the scope was synchronized to the trigger from the POD.

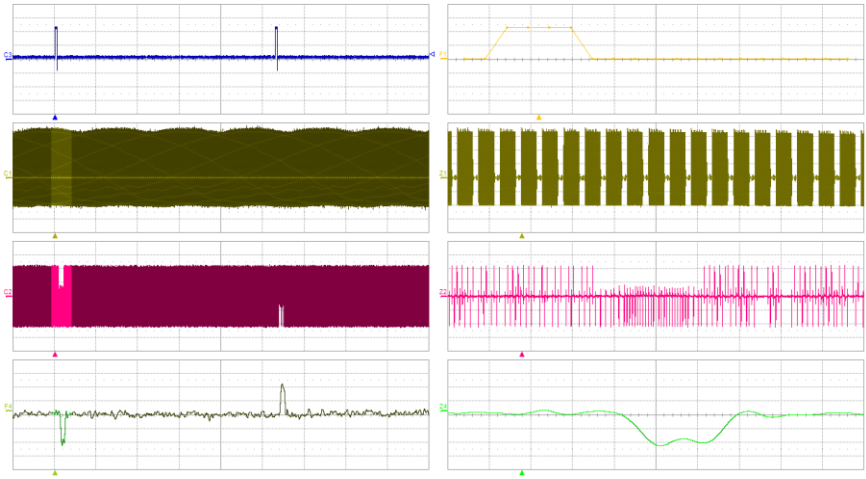

Figure 4.2 Screenshot of DACI stimulus verification setup. From top to bottom, left (20 ms trace, 2 ms per division): trigger (blue), captured RF (yellow), actuator output (purple), actuator output low-pass filtered with 10kHz (green); right (1 ms trace, 100 µs per division): decoded stimulus amplitude (orange), and zoomed versions of the left plots.

In the second step, the EEG analysis was replicated on the bench. The stimulus artifacts originating from the RF transmission were measured with electrodes in a 1 l bowl containing physiological saline solution (NaCl 0.9%), mimicking the electrophysiological human head. The coil of the speech processor was fixed against the bowl by a magnet directing the RF energy at the recording electrodes positioned under the surface of the saline solution. The positions of ground, active and reference electrode were fixed both relative to each other and to the RF coil. The same recording setup and amplifier settings as for the physiological EEG measurements were used.

In the last step, the velocity of the stapes prosthesis for different stimuli was measured with laser Doppler vibrometry (LDV, Laser head OFV534, Polytec Inc., Europe) and recorded by a Rohde and Schwartz UPV audio analyzer.

4.3.4 EEG analysis

The EEG signal was divided into epochs of 32 768 samples, resulting in an epoch length of 1.024 s. Each individual EEG measurement lasted about 6 minutes and was manually stopped after about 3500 epochs were recorded. Epochs with recording artifacts such as muscle movements and skin potentials were rejected

to prevent the erroneous detection of neural responses and the distortion of response properties. To this end, epochs were sorted by maximum peak-to-peak amplitude and the top 5% of the epochs (i.e., the ones with the highest peaks) were removed from the measurement. After recording artifact removal, the average evoked response was determined by non-weighted averaging of all remaining responses to both condensation (positive) and rarefaction (negative) clicks.

4.3.5 Experiments

In a first group of experiments, the correct functioning of the analog stimulation setup as described above was verified with the oscilloscope and on the bench. As unusual artifact patterns were observed for analog stimulation, pilot measurements were performed in-vitro. To confirm the RF transmission as the source of the stimulus artifacts, the actually transmitted RF frames for a given analog stimulus were recorded and analyzed in Matlab.

To avoid distortion of responses by the observed artifacts, all further experiments were performed with the direct stimulation setup. The setup was again verified on the bench and the linearity of the actuator peak amplitude for stimuli with different click widths and at different stimulus intensities was analyzed with LDV.

In three subjects, auditory evoked responses to 204 µs click trains in the 40 and 90 Hz range at different stimulus intensities were recorded. In the 40 Hz range, click trains with rates of 33 and 44 Hz were used. For the 90 Hz range, rates of 82 and 97 Hz were used. Stimulus artifacts were removed by linear interpolation of the EEG during a blanking period of 1.4 ms similar to the method used in Hofmann and Wouters (2012). The ASSR was obtained from the bin corresponding to the stimulation rate of the frequency spectrum of the average epoch. The response amplitude was determined as the absolute amplitude, and the response phase delay as the inverse phase of the frequency bin. To determine the delay introduced by the auditory system, the mean apparent latency (i.e., group delay) was calculated as the ratio of the differences of phase delay and stimulation rate divided by 2π (John & Picton, 2000) for corresponding measurements with different stimulation rates. Only measurements at stimulus intensities with significant responses at both

stimulation rates as determined by a one-sample Hotelling T^2 test (Hotelling, 1931; Hofmann & Wouters, 2010) were considered.

Electrophysiological thresholds were estimated from the amplitude growth functions per frequency range. A two-sample Hotelling T^2 test was used to compare the responses for the two stimulation rates and to determine the presence of a neural response (Hotelling, 1931; Hofmann & Wouters, 2012). Thresholds were determined by bracketing, i.e. as the mean between the last significant ($p < 0.05$) and the first insignificant response. Additionally, thresholds were also estimated by visual inspection of the ABR recordings by an experienced clinician, and latencies of peak V were determined (Lasky et al, 1987). Behavioral thresholds were obtained for 200 µs click trains at 40 Hz using the 6 last reversals of a 2-up 1-down adaptive procedure (van Wieringen & Wouters, 2001) and compared to the electrophysiological thresholds. Statistical correlations for the determined threshold were not calculated because of the small sample size.

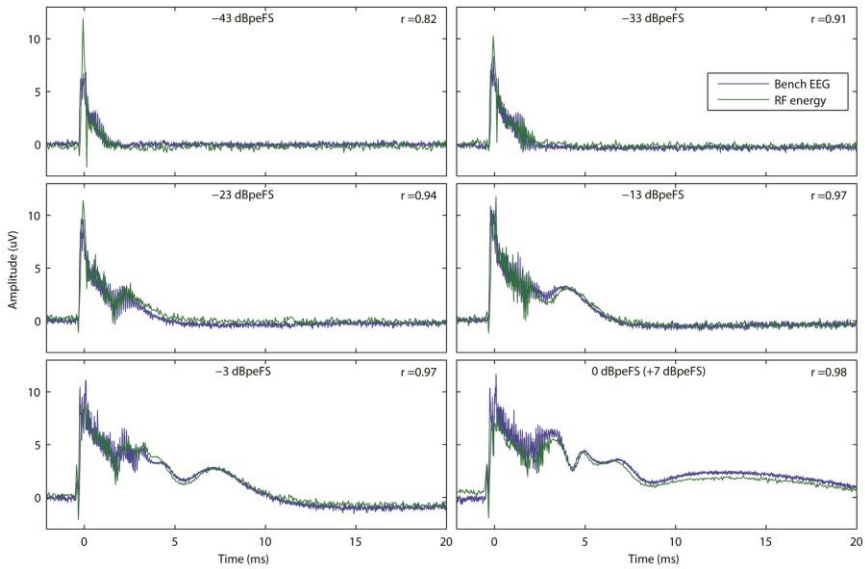

Figure 4.3 Bench test recordings of the stimulus artifacts with the analog stimulation setup for 200 µs click trains at different intensities: comparison between EEG recording (in blue) and the energy of the corresponding RF frames (in green). *P*: correlation coefficient. Measurement at +7 dBpeFS: clipped by firmware to 0 dBpeFS.

4.4 Results

4.4.1 Analog stimulation

After the verification of the analog stimulation setup with the oscilloscope, simulated EEG recordings of the stimulus artifacts for 200 µs click trains at different stimulus intensities were made on the bench without the actual implant or actuator present (Figure 4.3). While the click width was always fixed at 200 µs, the resulting stimulus artifacts differed in length between 2 and more than 15 ms for stimuli at -43 and 0 dBpeFS, respectively. The artifacts consisted of a sharp rise during the actual stimulating click, followed by a slow decay component and superimposed fast oscillations. For stimulus intensities of -13 dBpeFS and above, the slow decay component exhibited one or multiple peaks with a latency in the range of ABRs. To confirm the presence of similar stimulus artifacts in in-vitro recordings, pilot measurements for 100 µs clicks were performed in 3 subjects (see Figure 4.4 for an example). Again, similar stimulus artifacts could be observed, obscuring any possibly present neural response.

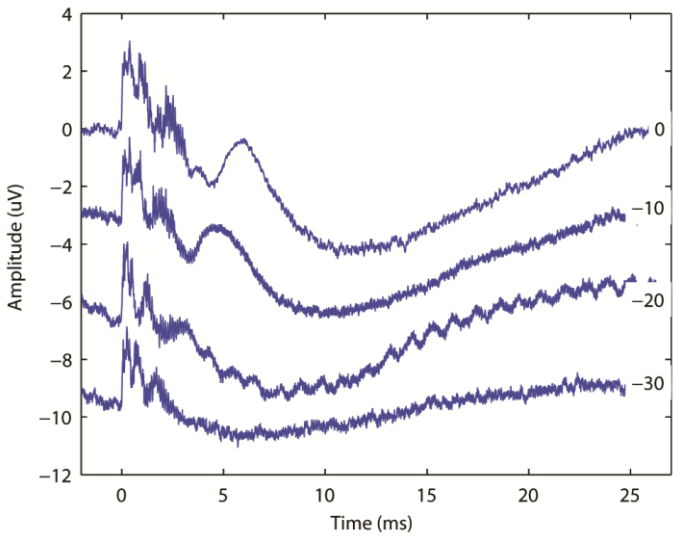

Figure 4.4 Recordings with subject S2 of possible neural response and stimulus artifacts with the analog stimulation setup for 100 µs 33 Hz click trains at different intensities (in equivalent dBpeFS).

As in-vitro artifacts were very similar to the ones already observed on the bench, the RF transmission was considered the most probable source of the artifacts. Recordings with the oscilloscope of the low-pass filtered RF signal revealed no low-frequency component that could have explained the observed artifact. To account for any non-linear demodulation effects in the saline solution, the ability of the root-mean-square (RMS) energy of the RF signal to predict the observed artifacts was explored (Figure 4.3). Depending on stimulus intensity, correlations between RMS energy of the RF signal and stimulus artifacts ranged from ρ=0.82 (-43 dBpeFS) to ρ=0.98 (0 dBpeFS), confirming the RF transmission as the most probable source of the stimulus artifacts.

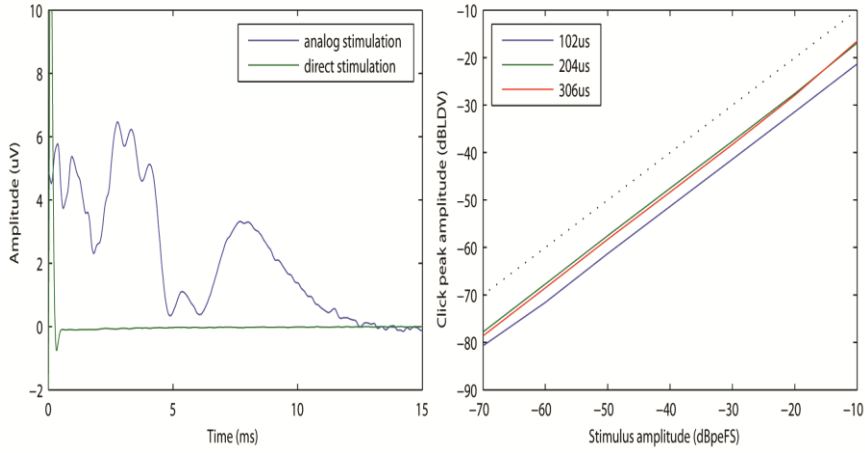

Figure 4.5 (**left** panel), Stimulus artifact for bench-test recording: difference between analog and direct stimulation setup for 200 µs click with equal intensity. (**right** panel), Amplitude growth function of the actuator as a relation between stimulus amplitude (3 different click trains of 102, 204 and 306 µs) and the actuator output measured with a LDV. A linear amplification is noted with this direct stimulation setup.

4.4.2 Direct stimulation

For the direct stimulation setup, bench recordings of 200 µs click trains resulted in stimulus artifacts with a constant duration of less than 0.3 ms below 2µV independent of stimulus intensity, in contrast to the artifacts of the analog stimulation setup which were much longer and varied in length (Figure 4.5, left

panel). LDV measurements of the oscillations of the stapes prosthesis on the bench in response to 102, 204 and 306 µs click trains at different stimulus intensities confirmed the linearity of the direct stimulation setup for stimuli with peak amplitudes between -70 and -10 dBpeFS (Figure 4.5, right panel). As the peak amplitudes of the 102 µs clicks were attenuated by about 4 dB compared to the peak amplitudes of the 204 and 306 µs clicks, all further experiments were performed with a click width of 204 µs.

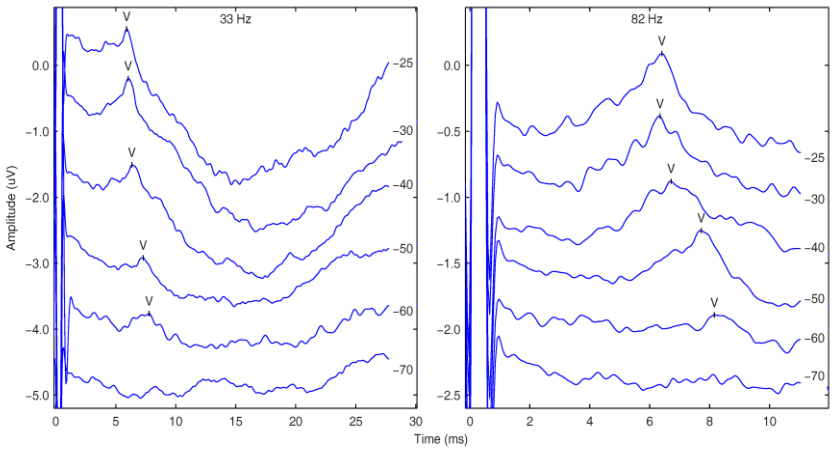

Figure 4.6 Response waveforms of subject S1 for 33 (**left**) and 82 Hz (**right**) click trains at different intensities (from -25 to -70 dBpeFS). Waveforms plotted with positivity at vertex upwards. Markers show ABR peak V as determined by an experienced clinician. Partial AMLR (Na/Pa) responses can be seen for the 33 Hz stimuli.

4.4.3 Response properties

Figure 4.6 shows representative examples of the time-domain response shapes in the 40 and 90 Hz ranges. Due to response filtering, the duration of stimulus artifacts increased to 1.4 ms in subjects, independent of stimulus intensity. Within the first 10 ms, ABR peaks V with variable amplitude and latency can be seen for both frequency ranges. At a stimulus intensity of -30 dBpeFS and stimulation rate of 33 Hz, peak V latencies were estimated at 6.03, 6.60 and 6.85 ms, for S1 to S3, respectively, which seemed to increase slightly with

stimulation rate up to latencies of 6.66, 6.85 and 7.28 ms at 97 Hz. For the 40 Hz responses, auditory middle latency responses (AMLRs) could also be recognized.

ASSR amplitude growth functions of all 3 subjects for the 40 Hz range are shown in Figure 4.7. Similar growth functions were recorded for the 90 Hz range (Figure 4.8). Response amplitudes grew monotonically and did not seem to reach saturation at the highest stimulation level in 64 out of 66 measurements (except for S1 at 33 and 97 Hz). Out of 66 measurements, 54 significant responses could be reliably recorded.

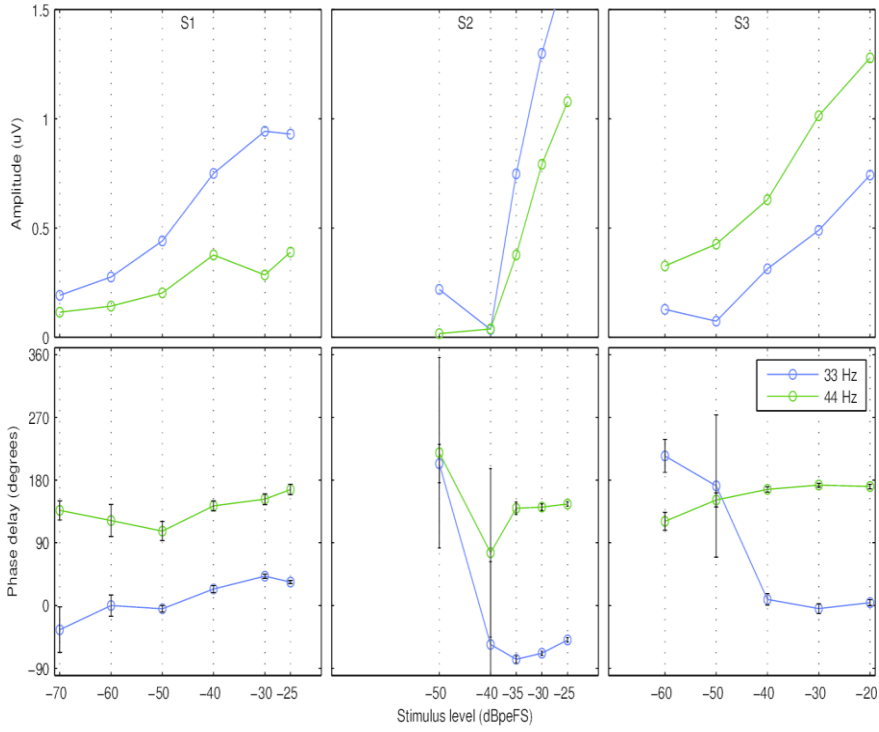

Figure 4.7 Response amplitudes and phase delay of all 3 subjects in the 40 Hz range. Stimulus intensity: in dBpeFS; error bars: phase delay change corresponding to the standard error of the response bin across epochs.

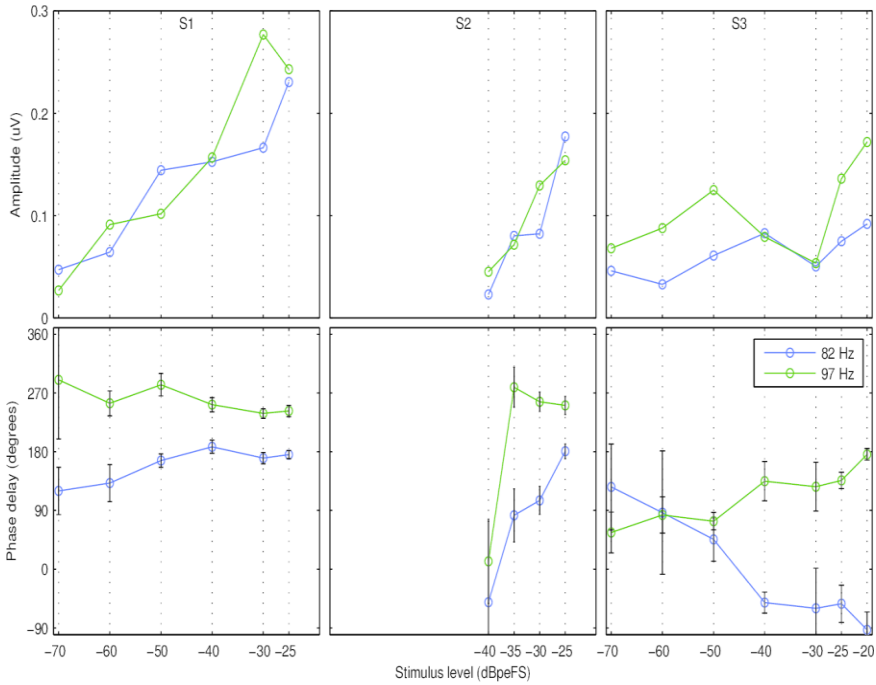

Figure 4.8 Response amplitudes and phase delay of all 3 subjects in the 90 Hz range. Stimulus intensity: in dBpeFS; error bars: phase delay change corresponding to the standard error of the response bin across epochs.

The mean amplitudes of all significant ASSRs for all stimulus intensities across subjects were 646 nV (interquartile range (IR) = 687 nV) and 531 nV (IR = 583 nV), for stimulation rates of 33 and 44 Hz, respectively. For the 90 Hz range, mean ASSR amplitudes for 82 and 97 Hz stimuli were 111 nV (IR = 90 nV) and 130 nV (median, IR = 89nV), respectively. Comparison between the two ranges showed higher ASSR amplitudes for the 40 Hz (mean 588 nV, IR = 618 nV) than for the 90 Hz range (mean 122 nV, IR = 85 nV). This difference was statistically significant (Wilcoxon signed rank test, $p < 0.001$).

The differences in phase delay between the two adjacent stimulation rates of all significant responses were calculated per frequency range (Figure 4.7 and Figure 4.8). The mean differences in phase delay were 128, 207 and 77 degrees for the 40 Hz range (frequencies 33 and 44 Hz) and 101, 139 and 207 degrees for the 90 Hz range (82 and 97 Hz), for S1 to S3, respectively. Again the difference between the two ranges was statistically significant (Wilcoxon signed rank test, $p = 0.003$). Mean apparent latencies were 39.9 ms (SD = 9.7 ms) and

24.7 ms (SD = 13.0 ms) for the 40 and 90 Hz range, respectively (Figure 4.9). Both for the 40 and 90 Hz range, higher response latency values were calculated for S2 and S3 than for S1, although the difference was statistically not significant ($p > 0.05$).

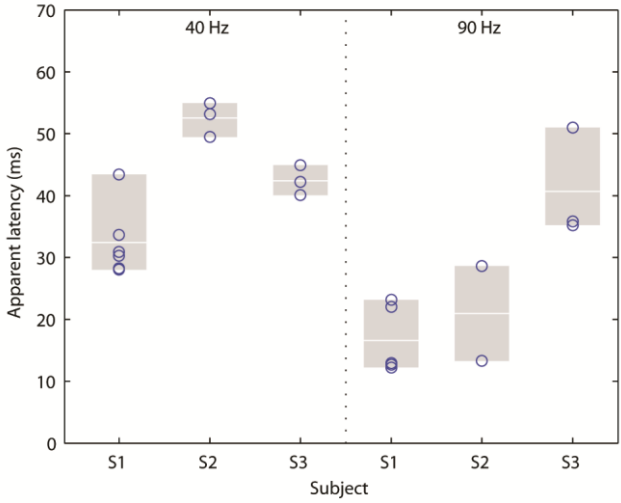

Figure 4.9 Individual apparent latencies for each subject in 40 Hz and 90 Hz range. Bars: minimum, maximum and mean latencies.

4.4.4 Thresholds

The estimated electrophysiological thresholds detected from the ASSRs as well as from the ABR peak V and their relationship with the behavioral thresholds at 40 Hz can be seen in Table 4.2. With the bracketing method, electrophysiological ASSR thresholds of -75, -38 and -65 dBpeFS for the 40 Hz range and -75, -38 and -45 dBpeFS for the 90 Hz range were determined for S1 to S3, respectively. Except for S3 in the 90 Hz range, these thresholds were the same for both frequency ranges. For ABR peak V, thresholds were -65, -35 and -35 dBpeFS for S1 to S3, respectively.

Table 4.2 Relationship between behavioral and electrophysiological thresholds obtained from ABRs and ASSRs. Thresholds: in dBpeFS; behavioral: at 40 Hz.

Subject	Behavioral	ASSR (40 Hz)	ASSR (90 Hz)	ABR peak V
S1	-87	-75	-75	-65 (Latency = 7.8 ms)
S2	-41	-38	-38	-35 (Latency = 6.6 ms)
S3	-87	-65	-45	-35 (Latency = 6.8 ms)

Behavioral thresholds were lower than electrophysiological thresholds, with differences of 12, 3 and 22 dB for thresholds based on 40 and 90 Hz ASSRs, and of 12, 6 and 52 dB based on ABR peak V, for S1 to S3 respectively. Mean differences between behavioral and electrophysiological thresholds were 12, 19 and 26 dB for electrophysiological thresholds based on 40 and 90 Hz ASSRs and ABR peak V, respectively.

4.5 Discussion

4.5.1 Analog and direct stimulation

Only a few other studies have investigated the use of auditory evoked potentials in acoustic hearing implants, none of them with digital speech processing devices. Verhaegen et al. (2010) reported ASSR measurements in 4 subjects with severe MHL for the intra-operative verification of a floating mass transducer (FMT) placement. Subjects were implanted with a MED-EL Vibrant Soundbridge device (VSB), using a 404 analog audio processor driven by an audiometer. As the measurements were relative (i.e., ASSR thresholds with a certain FMT coupling compared to those with another coupling), the authors stated that the calibration of the setup was of minor importance and no specific reporting on the artifacts was provided. In contrast to the DACI, the VSB device relies on analog sound transmission based on amplitude modulation, which could partially explain the difference in the observed artifacts. In temporal bone specimens, Radeloff et al. (2011) identified artifacts, occurring at 40 dB HL and above, which arose from electrical cross-talk of the FMT during electrocochleography (ECoG) using broad spectrum clicks and sinusoidal tone bursts. Averaging of responses to rarefaction and condensation stimuli resulted

in a significant reduction, with a remaining artifact arising from asymmetrical signals. The analog transmission resulted in linear growth of the artifacts, and no artificial signal was identified mimicking the typical shape of compound action potentials in their 3 subjects. A third study investigated the role of intra-operative ECoG to optimize the placement of the FMT of the VSB on the round window membrane in subjects with conductive and MHL (Colletti et al, 2012). Relative ECoG measurements using alternating clicks were recorded during FMT placement, demonstrating a reduced latency and higher amplitude of the compound action potential in the case of a better coupling of the FMT to the round window membrane. While such measurements might intra-operatively be also applicable for DACIs, certainly to analyze the coupling to the cochlea, postoperative ECoG measurements remain difficult to perform due to the invasive character of the measurement. Due to middle ear changes, causing mixed hearing loss, postoperative electrode placement could be complex and cause local damage. Additionally, ABRs and ASSRs provide information about the auditory pathway from the VIIIth nerve up to the auditory cortex that cannot be obtained from ECoG measurements.

In the current study, it was found that the stimulus artifacts for the investigated DACI were related to the energy of the RF transmission. In contrast, the actuator did not seem to interfere with the EEG recordings. With the analog stimulation setup, the non-linear stimulus artifacts were much longer than the theoretical click stimuli and obscured any possibly present neural responses. The stimulus artifacts were directly linked to the RMS energy of the corresponding RF frames, suggesting that the actual stimuli extended beyond the monophasic clicks. This was confirmed by the decoding of the transmitted sample values in the RF signal, which showed a slow delay component of the actual stimuli with a similar length as the artifacts themselves. As inspection of the audio signal, provided to the personal audio cable accessory of the sound processor, showed stimuli that were very close to ideal clicks, the source of this effect is most likely found either in the circuitry in the cable or the signal processing hardware of the speech processor.

Because of these limitations, the proposed direct stimulation setup was developed. By using a digital path that converts the stimulus directly into the corresponding RF frames, any non-linear effects because of, e.g. the sample

coding, are only present during the stimulus clicks, with enough time between the stimuli to record the neural responses. For ASSRs, time-domain interpolation of the EEG signal for the duration of the artifacts allows the recovery of the undistorted neural responses.

In clinical practice with unaided stimulation, click stimuli for ABR and ASSR measurements most commonly use a click width of 100 µs. Beattie and Boyd (1984) showed that latencies increased approximately 0.1 ms as duration increased from 100 to 200 µs. In the current study, stimulation by a Codacs DACI even with the direct stimulation setup resulted in attenuated peak amplitudes for stimuli with a click width of 104 µs when compared to the theoretical amplitude as seen for longer click widths. As such a click width corresponds to only two samples at the internal sample rate of 19607 Hz, this is most probably caused by the actuator impulse response characteristics. The selected click width of 204 µs resulted in clearly recognizable ABR peaks V for most subjects, but more work is needed to determine the optimal stimulation settings for aided ABR recordings with such a device.

4.5.2 Response properties and thresholds

With the direct stimulation setup, ABRs and ASSRs could be reliably recorded. ABR peaks V were clearly recognizable in the 40 and 90 Hz range, but latencies were longer than for normal hearing subjects. This might be partially explained by a cochlear impairment, certainly in the basal (high-frequency) portion of the cochlea (Yamada et al, 1979). The different ages and degrees of hearing loss of the three subjects tested might also account for some peak V latency variability (Jerger & Hall, 1980; Debruyne, 1986). Standardized ABR peak V latencies obtained by aided stimulation with acoustic hearing implants are currently lacking in the literature. Overall, the recording and analysis of ABRs under general anesthesia seems feasible for future implantations.

ASSR amplitudes were similar to amplitudes for responses to electrical CI stimuli (Hofmann & Wouters, 2012), and amplitudes were larger in the 40 Hz than the 90 Hz range. Amplitudes increased non-linearly with increasing stimulus intensity (Lins et al, 1995). The mean response latency of 39.9 ms for the 40 Hz range is in accordance with the latency of acoustically evoked ASSRs in response to clicks, e.g. 33.3 ms (SD = 8.6 ms, 35 to 55 Hz) and 41.1 ms (SD = 5.7 ms, 29 to

54 Hz) (Stapells et al, 1984, 1987), and the latency of electrically evoked ASSRs in response to low-rate pulse trains of 35.6 ms (SD = 5.3 ms, 35 to 47 Hz) (Hofmann & Wouters, 2010). In the 90 Hz range, the mean response latency of 24.7 ms is slightly longer than the latencies found for acoustically evoked ASSRs in literature, e.g. 15.7 to 22.0 ms (80 to 92 Hz) for beats or 16.1 to 20.7 ms (81 to 95 Hz) for amplitude-modulated stimuli (John & Picton, 2000; Purcell et al, 2003). It is longer than the one found for electrically evoked ASSRs of 12 ms (79 to 91 Hz), which could only partly be attributed to the mechanical transmission in the cochlea (Hofmann & Wouters, 2010; Purcell et al, 2003). As shown in Figure 4.9, within-subject variability was low, except for one value in the 90 Hz range for S3. For both frequency ranges, the found latencies allow the estimation of the predominant neuronal generator, with 40 Hz responses most likely originating beyond brainstem and 90 Hz responses originating in the brainstem, further confirming the correct measurement of the neural responses (Picton et al, 2003). In the future, measurements for a larger number of DACI-aided subjects might allow setting of standardized values according to hearing loss.

In general, response properties were in line with the hearing characteristics of the subjects, e.g. S2 showed a steeper response amplitude growth across a smaller clinical dynamic range in comparison to the other two subjects. No correlation coefficients could be calculated between behavioral and electrophysiological thresholds due to the small sample size, but differences of 12, 3 and 22 dB, for S1 to S3, are in line with data obtained for unaided stimulation (Herdman & Stapells, 2001). In the field of acoustic hearing implants, we are not aware of any other study that has reported on absolute threshold determination with evoked potentials. Comparing behavioral and electrophysiological thresholds, differences were lowest for ASSRs in the 40 Hz range and for 2 out of 3 subjects in the 90 Hz range, followed by ABR peak V, where the detection of ABR peak V proved difficult especially for lower signal-to-noise ratios.

4.6 Conclusion and future research

This study demonstrated for the first time that auditory evoked potentials could reliably be recorded and analyzed in patients with a digital speech processing DACI. The proposed direct stimulation setup minimized interference because of stimulus artifacts and allowed the recording of ABRs as well as 40 and 90 Hz ASSRs, with response properties and electrophysiological thresholds that were similar to those reported in the literature.

Future research includes recording intra-operative feedback of direct cochlear acoustical stimulation and the automatic post-operative determination of preliminary fitting parameters. Methods need to be developed to reduce the recording time, rendering this method feasible for intra-operative measurements. As the current study focused on feasibility, in future, a higher number of subjects needs to be tested before clinical implementation is readily available. The use of narrow-band stimuli such as tone bursts (Stapells et al, 1984) could allow the recording of more frequency specific responses. As the indication criteria extend to profound MHL, the further development of the proposed techniques might provide an objective measure for the adequate coupling to the inner ear, but also for the correct auditory processing in the cochlea and brainstem for difficult differential diagnosis cases. Absent electrophysiological responses indicating insufficient cochlear reserve during intra-operative measurements in such cases could pose an indication to convert the surgery to a cochlear implantation. The authors feel that sharing this insight early at this stage of direct acoustic cochlear stimulation development will greatly improve near future clinical and translational research.

4.7 Acknowledgements

We are grateful to our subjects. Part of this research was supported by IWT (Institute for the Promotion of Innovation by Science and Technology in Flanders) project 110722 and by Cochlear Ltd. N. Verhaert was supported by the Research Foundation Flanders and the Research Council of the University Hospitals Leuven.

Chapter 5
Is the lateral semicircular canal a coupling site for direct acoustic cochlear stimulation?[7]

5.1 Abstract

Objective: Various etiologies of severe to profound mixed hearing loss are associated with difficulties for adequate hearing rehabilitation. Recently, promising results for speech understanding in quiet and noise were obtained with a direct acoustic cochlear implant (DACI). Its surgical implantation may be regarded as challenging, however, certainly in the case of chronic otitis media. Straightforward, reproducible acoustic stimulation of an anatomically easy accessible inner ear site is desired and could reduce surgical risks and possibly extend current indications of DACI. In this experimental study, the possibility of DACI stimulation of the intact, blue-lined and opened lateral semicircular canal (LC) was investigated and compared with standard oval window coupling. Round window (RW) velocity, as a measure of the performance of the device and its coupling efficiency, was determined in fresh-frozen human cadaver heads using a laser Doppler vibrometry setup. From these measurements, equivalent sound pressure level (L_E) output was calculated. The surgical coupling technique was also described. Results for the different conditions obtained in 5 heads were analyzed in 3 frequency ranges: low (0.1-0.8 kHz), middle (0.8-2.5 kHz) and high (2.5-8 kHz). With *LC opened* stimulation, a maximum L_E of 126 equivalent dB SPL (SD = 10 dB) was reached, comparable to

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the *standard* oval window DACI position (127 dB SPL, SD = 21 dB). Pairwise comparisons revealed that RW velocity was significantly lower in the *LC intact* condition than in the *standard* condition in the low and middle frequency range, confirming the added value of direct acoustic inner ear stimulation. L_E analyses showed modest but significant added value of the *LC blue-lined* condition over the *LC intact* condition for the low and high frequency range. In the *LC opened* condition, higher RW velocity was obtained than in *LC intact* or *blue-lined* conditions for all frequency ranges. The effect of an induced stapes footplate fixation was also investigated. L_E analyses showed no significant difference between *LC opened* and *LC opened with stapes fixation* conditions in the middle and high frequency ranges. These results demonstrate for the first time that the LC may be a potential site for direct acoustic stimulation, even in case of stapes footplate fixation. Future studies need to address long-term in vivo effects of LC stimulation and their impact on cochlear micromechanics and vestibular system.

5.2 Introduction

In the past decade, considerable temporal bone and human clinical research has been conducted on the efficiency of acoustic hearing implants, such as active middle ear implants (AMEIs) and direct acoustic cochlear implants (DACIs), in several anatomical sites. Although initially proposed for sensorineural hearing loss, most acoustic hearing implants are currently used for conductive or mixed hearing loss. Because they are indicated for various pathologies, many different ways of implantation have been described, each with its own advantages and disadvantages (Martin et al, 2009; Baumgartner et al, 2010; Häusler et al, 2008; Schwab et al, 2012; Luers et al, 2013; Tringali et al, 2010; Verhaert et al, 2011). Recently, a systematic review of clinical results was published on this subject, demonstrating a certain degree of variability in functional outcome (Verhaert et al, 2013a). With the introduction of titanium couplers, this non-uniformity could potentially be reduced (Luers et al, 2013), but dislocation of a non-fixed stimulator with loss of amplification remains a possibility (Bernardeschi et al, 2011).

For severe to profound mixed hearing loss, only powerful implants can produce sufficient output to stimulate the remaining cochlear reserve. A Codacs DACI device produces high output, thereby achieving encouraging speech perception results, even compared to the best conventional treatments, such as hearing aids (Lenarz et al, 2014; Zwartenkot et al, 2014). The surgical procedure is often regarded as challenging, as it involves posterior tympanotomy, fixation of the transducer inside a small mastoid cavity, and then a transmastoid or endaural approach for stapedotomy with coupling of a stapes prosthesis to an actuator (Lenarz et al, 2013). Taking into account its initial phase, the average time of surgery was around 3.5 hours (communication from the manufacturer) and the approach carries risks of facial nerve exposure or damage to residual hearing, well known from cochlear implant surgery and stapes surgery in case of advanced otosclerosis or tympanosclerosis (Vincent et al, 2002). Straightforward, reproducible acoustic stimulation of an anatomically easy accessible inner ear site could reduce these risks associated with middle and inner ear implant surgery. Driving the cochlea at other sites, such as a 'third-window', has been proposed experimentally in an animal model (Lupo et al, 2012) and implemented in selected cases, where neither the oval window nor round window (RW) could be reached (Pau & Just, 2010). The aim of this experimental study was (1) to investigate the feasibility of acoustic stimulation of the lateral semicircular canal (LC), (2) to develop an adequate surgical technique, and (3) to assess coupling efficiency compared to standard oval window coupling, as described by Lenarz et al. (2013). Experiments were performed in fresh-frozen human cadaver heads to obtain data mimicking an in vivo context as closely as possible.

5.3 Methods

5.3.1 Human cadaver temporal bone preparation

Fresh frozen cadaver heads were used for this experiment. Six entire heads were evaluated after obtaining authorization to use organs and tissues for research (Science Care, Inc., Phoenix, AZ, USA). The medical history of each head was provided by the supplying company. After thawing, all experiments

were performed within an 8-hour period and the heads were rinsed meticulously to prevent mechanical changes due to dehydration during the experiments. Microscopic visual inspection was carried out to verify temporal bone integrity and quality, as well as the absence of otologic disease, as recommended in the ASTM standard practice (ASTM, 2005). The study was approved by the local ethics committee.

Surgical preparation consisted of a canal wall-up mastoidectomy, with preservation of the posterior border of the mastoid cavity for placement of the implant's fixation system. The facial recess was opened through a large posterior tympanotomy to achieve exposure of the stapes crura, stapes footplate and the round window membrane (RWM), with removal of its secondary mucosal membrane. Care was taken not to alter ossicular chain integrity. Visual inspection was performed to check for perilymph leakage. One head (1/6), considered for training purpose, was excluded from further analysis, as drilling of the LC accidently led to perilymph evaporation. The heads were firmly held in a holding block during all procedures.

5.3.2 Acoustic hearing implant

Throughout this study, the driving force for acoustic stimulation was an electromagnetic actuator, which is part of an acoustic hearing implant, the Codacs™ DACI system (Cochlear™ Ltd. Sydney, Australia). This system was recently CE-approved and made commercially available for clinical use, indicated for severe to profound mixed hearing loss. The surgical procedure to implant the DACI system was previously described in detail (Lenarz et al, 2013). In brief, following the manufacturer's specifications, the actuator's artificial incus (1 mm diameter), or rod, is connected to a conventional stapes prosthesis coupled to the perilymph of the inner ear at the level of the oval window niche. Coupling to the inner ear is done after removal of the stapes superstructure, i.e. stapedotomy or stapedectomy. For clinical application, a calibrated-hole technique using a laser or skeeter burr is preferred for stapedotomy. In temporal bone experiments, stapedectomy with complete removal of the entire footplate and placement of fibrous tissue for oval window sealing is more feasible. This is consistent with the first DACI implantations, as described by Häusler et al. (Häusler et al, 2008). Previous investigations have confirmed

linearity of actuator output up to 1 V root mean square (RMS) (Verhaert et al, 2014a), potentially limiting non-linear vestibular effects.

5.3.3 Measurement setup

An insert earphone (ER-2, Etymotic Research, USA) was fixed inside the external ear canal with adaptive foam to seal it externally. The tube of a probe microphone (ER-7C, Etymotic Research, USA) was positioned within 1-2 mm of the tympanic membrane and used as a reference. The insert earphone assembly was calibrated before each use. The earphone was driven by a sine sweep at approximately 94 dB SPL between 100 and 10000 Hz generated by an audio analyzer (UPV, Rhode and Schwartz, Munich, Germany). For velocity measurements, a Zeiss microscope-mounted laser Doppler vibrometry (LDV) system (OFV5000 Vibrometer Controller, OFV-534 Compact Sensor Head and A-HLV MM 30 Micromanipulator; Polytec GmbH, Waldbronn, Germany) was utilized. To enhance light reflection, markers made from small pieces of reflective tape (0.5 mm^2) were placed on the posterior stapes crus and RWM. Anatomical preparation ensured an optimal laser angle of about 70- 80° to the RWM and posterior crus of the stapes. The LDV controller was set to 10 mm/s/V with a 100 kHz low-pass and 100 Hz high-pass filter.

Stapes and RW velocity were evaluated with closed-field acoustic measurements in a quiet room to check the temporal bone quality. Obtained middle ear transfer functions (H_{TV}) were calculated as previously described (ASTM, 2005). To quantify the performance of a device coupled to the ossicles, a method calculating equivalent sound pressure levels (L_E), in equivalent dB SPL, and maximum equivalent sound pressure levels ($L_{E,max}$) from sound-induced stapes velocity was developed by Rosowski et al. (2007). Unlike with RW-driven AMEIs (Tringali et al, 2010), computing the electrovibrational transfer function (H_{EV}) of the stapes was not possible, as during standard DACI implantation the stapes superstructure is removed and the cochlea is driven by a conventional stapes prosthesis. Therefore, as in the procedure described by Chatzimichalis et al. (2012), output was derived from RWM velocity measurements, expressed in dB m/s. Stimulation of 1 V RMS was applied directly to the actuator. The audio analyzer simultaneously captured stapes or RW velocity output from the LDV and probe microphone signals near the tympanic membrane. In general, the

recommendations as in the ASTM practice were followed for specimen preparation, measurement setup and analysis, however, whole heads were used mainly for intra-head comparisons, and thus a minimal deviation regarding the velocity criteria range was regarded as acceptable.

5.3.4 Experiments

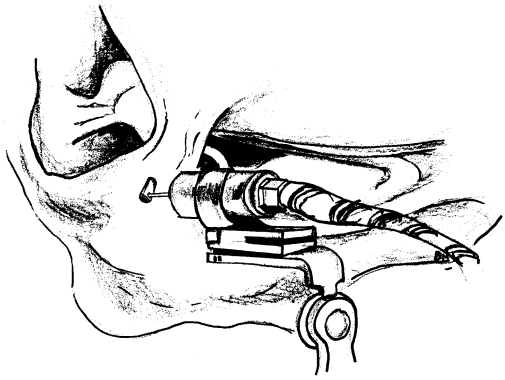
After quality control, each cadaver head was implanted with a DACI coupled to the inner ear in 5 consecutive conditions, as illustrated in Figure 5.1. The same investigators conducted each experiment, reducing variability. RW velocity was measured at a similar angle for each condition. Three repetitive LDV measurements were carried out for each velocity measurement. In each of the first four conditions, contact between the actuator's artificial incus and the coupling site was made neither applying too much pressure on the surface nor impeding a correct movement of the rod.

Condition 1 – *LC intact*: The actuator was approximated against an intact LC easily accessed through a basic mastoidectomy, keeping the ossicular chain and buttress intact. Contact was made at the dome of the LC, posterior to the ampulla.

Condition 2 – *LC blue-lined*: Using a 0.5-mm diamond burr and intermittent irrigation the LC was blue-lined, indicating imminent appearance of the endosteum of the labyrinth, similar to posterior canal occlusion (Parnes, 1996). Again, the actuator was approximated against the blue-lined surface, without breaching it.

Condition 3 – *LC opened*: The canal was opened further (size 0.5 x 0.7 mm) until the last endosteal bone shell could be gently fractured with a fine spatula, keeping the membranous labyrinth intact. This was defined as a canalotomy. The surgical technique was inspired by the early fenestration operation described by Sourdille and Lempert, although the endosteal flaps were not folded back (Shambaugh & Wiet, 1979; Farrior & Rophie, 1985). At this point, no perilymph aspiration was performed. The opening was directly covered with fibrous tissue obtained from the temporalis fascia. The actuator's artificial incus was gently brought into contact in a perpendicular manner (Figure 5.1 a,b).

a



b

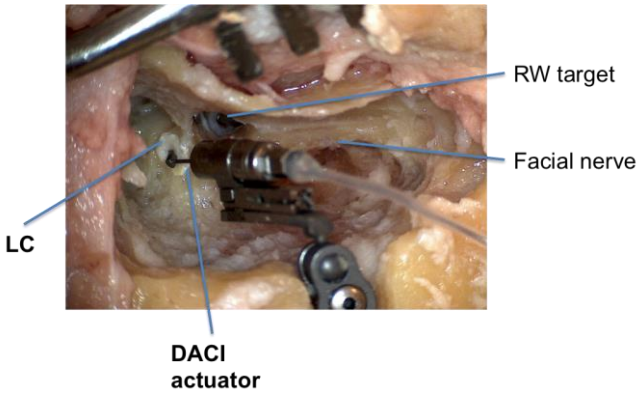


Figure 5.1 Coupling of DACI actuator with its artificial incus to the lateral semicircular canal (LC). (**a**) Schematic illustration demonstrating the perpendicular position of the actuator's tip (diameter of 1 mm) to the LC. Posterior tympanotomy is drawn for illustrative reasons. (**b**) Fresh head preparation showing LC stimulation (*LC opened* condition) with fascia interposition, view from posterior with reflective mirror on RWM. Note the proximity of the facial nerve with the narrow access to the oval window.

Condition 4 – *LC opened with stapes fixation*: After completing condition 3, stapes footplate fixation was achieved using techniques previously described for the dental acrylic application (Nakajima et al, 2005; Devèze et al, 2010). Thus, LC stimulation could be investigated in case of stapes fixation, similar to otosclerosis pathology, as this is one of the principal clinical indications for DACI implants. The LDV was used to measure stapes velocity attenuation at the stapes posterior crus (4 heads) and/or the RWM (3 heads).

Condition 5 – *Standard*: After elimination of any dental acrylic surplus, the entire stapes was removed without suction and fibrous tissue was immediately

placed to seal the oval window. The footplate was removed for reasons of reproducibility and to avoid footplate manipulations. The actuator of the DACI implant was then introduced through the opening of the posterior tympanotomy and placed about 4-6 mm above the oval window. A conventional stapes prosthesis, titanium K-Piston type, 0.6 mm in diameter with a loop (Heinz Kurz GmbH, Dusslingen, Germany), was placed on the fibrous tissue in the oval window and firmly crimped to the actuator. The fascia was maintained on the canalotomy to avoid leakage.

After checking for normality, data were statistically analyzed using paired samples t-tests, with RW velocity as a dependent variable. Third octave band frequencies were analyzed represented by the center frequency in the figures. Analyses were separately performed for each frequency range using the geometric mean (low, 0.1-0.8 kHz; middle, 0.8-2.5 kHz; high 2.5-8 kHz), and comparisons were made between the given conditions. Similar to Tringali et al (2010), these three frequency ranges were chosen to investigate the coupling in three clinically relevant ranges. For all analyses, an effect size (*r*) was calculated using Equation 1, derived from the *t*-value and degrees of freedom (d*f*) (Rosnow & Rosenthal, 2005).

Equation 1

$$r = \sqrt{\frac{t^2}{t^2 + df}}$$

In a first step, *LC intact*, *LC blue-lined* and *LC opened* conditions were compared with each other and with the *standard* condition. In a second step, the additional effect of stapes fixation on top of the *LC opened* condition was investigated (*LC opened with stapes fixation*). After RW velocity analyses, data were re-analyzed taking account of individual variance of cadaver head mobility, using L_E measurements as a dependent variable. Only outcomes that differed from RW velocity analyses were reported.

5.4 Results

5.4.1 Closed-field acoustic transfer functions

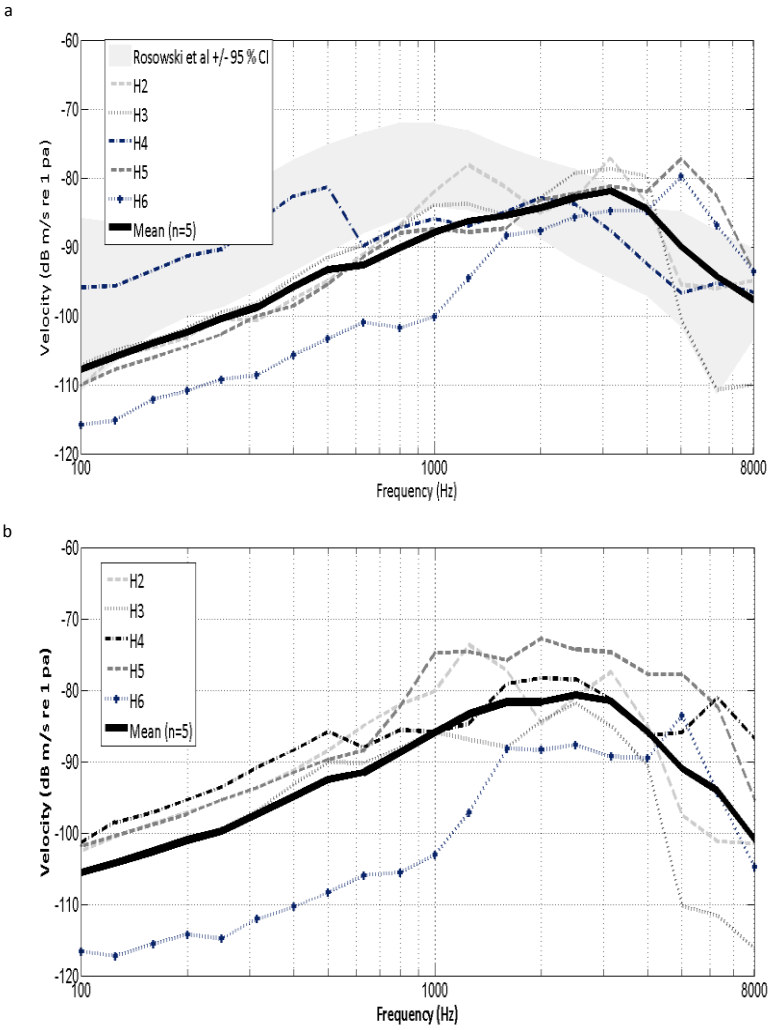


Figure 5.2 Closed-field acoustic middle ear transfer function (H_{TV}) at the stapes (**a**) and the RWM (**b**) in 5 human heads (in dB m/s normalized to 1 Pa). Additionally in panel a, as a gray shaded region, the mean and +/- 95% CI of H_{TV} measured in a large population of temporal bones is shown, as reported by Rosowski et al. (2007).

H_{TV} was computed in units of dB m/s normalized to acoustic input pressure (Pa) (ASTM, 2005). Figure 5.2 depicts stapes and RW velocity as individual curves

obtained with a sine signal for each cadaver head, plotted against the range, as described by Rosowski et al. (2007) for temporal bones. Both stapes and RW transfer functions were comparable. At 1.6 kHz, a mean stapes velocity of -85.8 dB m/s was in line with findings of previous studies. For RW velocity, a peak of -81.7 dB m/s was measured at 1.25 kHz, with a second similar peak around 2.5 kHz. Although a mean stapes velocity in the low frequency range was slightly below (<3.5 dB) the 95% confidence interval (CI) of the accepted range (Rosowski et al, 2007), these heads were included because the main goal in this experimental study was to investigate relative intra-head comparisons for different coupling strategies, as mentioned previously.

5.4.2 LC stimulation

Coupling of the actuator to the LC was investigated at 1 V RMS through the output measured at the RWM level in terms of RW velocity. Figure 5.3 shows the mean RW velocity of 5 heads plotted in the frequency domain for the different experimental conditions. Measurement variability per condition per head was very low (0.8 dB for 3 repetitions) and therefore the average value was used. *LC intact* and *LC blue-lined* conditions yielded similar findings, with an RW velocity above noise level (not shown), but well below output in the *standard* condition, especially in the low and middle frequency range. Means, standard deviations and peak values in 3 adjacent frequency ranges (with geometric means per frequency range) for the 5 different conditions are detailed in Table 5.1. Statistical analysis confirmed that obtained RW velocity data were normally distributed for all conditions. Conditions were compared using paired samples t-tests, as mentioned before.

RW velocity was significantly lower in the *LC intact* condition than the *standard* condition in the low ($t(4)= -5.34$, $p= .006$, $r= .94$) and middle ($t(4)= -4.28$, $p= .013$, $r= .91$) frequency range, confirming the added value of direct acoustic inner ear stimulation. The same trend was observed for the high frequency range, but it was not statistically significant ($t(4)= -1.72$, $p= .16$, $r= .65$). There was no impact of blue-lining on coupling efficiency (*LC intact* vs. *blue-lined* conditions) in the low and middle frequency ranges (low: $t(4)= -.60$, $p= .58$, $r= .29$; middle: $t(4)= -1.00$, $p= .37$, $r= .45$). In the high frequency range there was a significant difference ($t(4)= -4.23$, $p= .013$, $r= .90$).

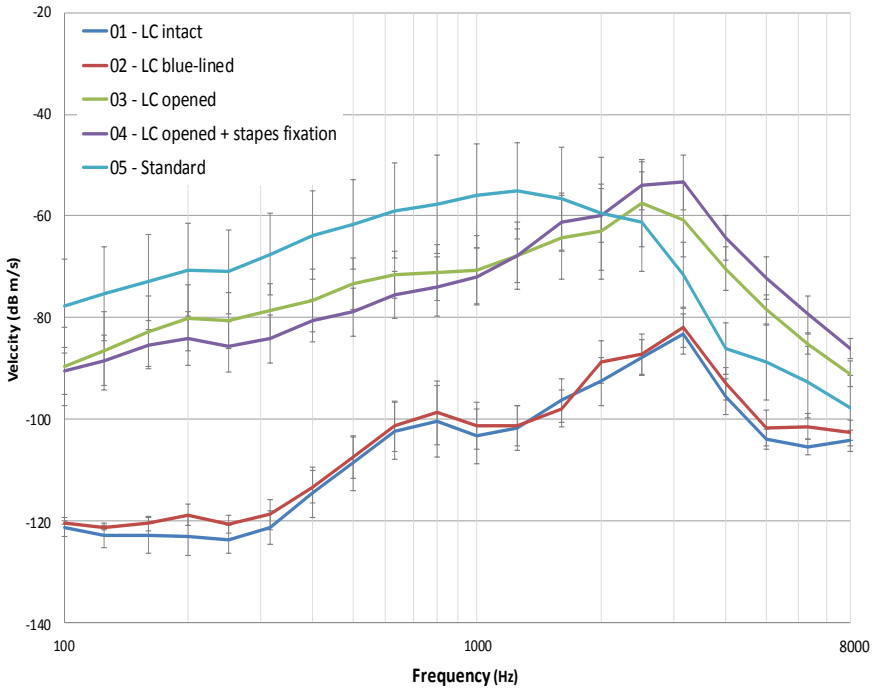


Figure 5.3 Performance of the DACI in different coupling positions, mean velocity (dB m/s) measured at RWM (n=5), with error bars as standard errors.

Table 5.1 Mean (n=5), standard deviation (SD) of RW velocity for the 3 frequency ranges and peak value over all frequencies for the 5 measurement conditions (in dB m/s re 1 Pa).

Condition	Low		Mid		High		Peak	
	Mean	SD	Mean	SD	Mean	SD		SD
LC intact	-105.6	12.8	-90.8	7.3	-88.4	7.6	-78.0	8.6
LC blue-lined	-103.8	9.7	-90.1	8.1	-86.8	7.5	-79.6	6.6
LC opened	-75.2	11.4	-60.9	17.8	-65.2	11.8	-58.5	17.3
LC opened + stapes fixation	-79.2	11.3	-57.9	10.0	-59.6	11.6	-56.5	17.0
Standard	-63.2	20.4	-56.6	22.1	-78.2	14.3	-55.7	19.4

When comparing *blue-lined* and *standard* conditions, the findings were unsurprisingly similar to the *LC intact* condition. Here again, results were

significant in the low (t(4)= -6.28, *p*= .003, r= .95) and middle (t(4)= -4.43, *p*= .011, r= .91) frequency range, and the same trend, though not significant, was found for the high (t(4)= -1.53, *p*= .20, r= .61) frequency range.

In the *LC opened* condition, higher RW velocity was obtained than in the *LC intact* condition for all frequency ranges (low: t(4)= -14.39, p= .001, r= .99; middle: t(4)= -3.36, *p*= .028, r= .86; high: t(4)= -4.24, *p*= .013, r= .90). The same advantage of the *LC opened* condition was found compared to the *LC blue-lined* condition (low: t(4)= -17.54, *p*= .001, r= .99; middle: t(4)= -3.32, *p*= .030, r= .86; high: t(4)= -4.06, *p*= .015, r= .90).

Both *LC opened* and *standard* conditions appeared to have an advantage over *LC intact* and *blue-lined* conditions. There was no indication of any difference in performance of the DACI coupled to the LC or the oval window (low: t(4)= -1.86, *p*= .137, r= .68; middle: t(4)= -.55, *p*= .609, r= .27; high: t(4)= 1.74, *p*= .156, r= .66).

5.4.3 Stapes fixation

Stapes footplate fixation resulted in loss of stapes velocity, with an average attenuation of 12 dB (SD = 7 dB) at the stapes (4 heads) and 15 dB (SD = 8 dB) at the RW (3 heads), measured via acoustic stimulation. The paired samples test revealed a significant difference in stapes velocity in the middle frequency range (*p*=.001), but not in the low or high range. Figure 5.4 shows mean and individual attenuation in H_{TV} obtained at the stapes.

The *LC opened with stapes fixation* condition investigated the influence of induced stapes fixation on LC stimulation with the DACI. Figure 5.3 depicts mean RW velocity in the frequency domain for this condition, plotted against the other experimental conditions. The paired samples t-test between the *LC opened* condition and the *LC opened with stapes fixation* condition suggested added value of the latter in the low frequency range (t(4)= 3.23, p= .032, r= .85). RW velocity was similar in the middle (t(4)= -.536, p= .62, r= .26) and high (t(4)= -1.12, *p*= .32, r= .49) frequency range. Similarly to the LC opened condition, higher RW velocity was found in the *LC opened with stapes fixation* condition compared to the *LC intact* condition (low: t(4)= -11.25, *p*= .001, r= .98; middle: t(4)= -4.55, *p*= .010, r= .92; high: t(4)= -4.23, p= .013, r= .90) and *LC blue-lined* condition (low: t(4)= -12.86, *p*= .001, r= .99; middle: t(4)= -4.33, *p*= .012, r= .91;

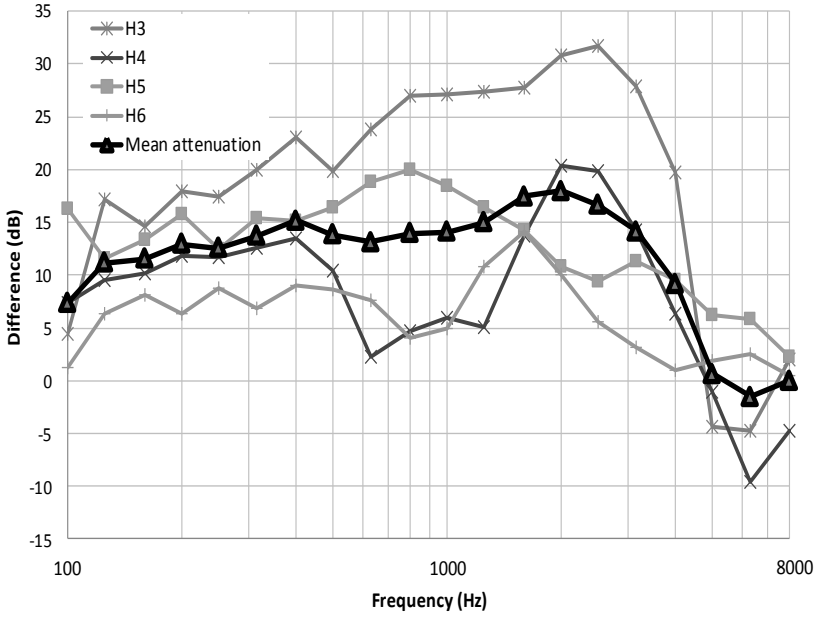


Figure 5.4 Experimental induced stapes footplate fixation (n=4) shown as mean attenuation of H_{TV} for stapes velocity (difference relative to velocity, in dB).

high: t(4)= -3.99, *p*= .016, r= .90). Direct comparison between the *standard* condition and the *LC opened with stapes fixation* condition also revealed no difference in terms of performance, similarly to the *LC opened* condition.

5.4.4 Equivalent sound pressure level

Figure 5.5 demonstrates mean L_E and $L_{E,max}$ obtained for all 5 conditions in 3 frequency ranges. With a peak value of 95.8 equivalent (eq.) dB SPL (SD = 17.9 dB) in the *LC intact* condition, DACI stimulation performed less well than expected compared to the *standard* position ($L_{E,max}$ of 126.9 eq. dB SPL, SD = 20.6). Blue-lining the LC yielded improved output, reaching 105.4 eq. dB SPL (SD = 11.4 dB). With *LC opened* stimulation, an $L_{E,max}$ of 126.2 eq. dB SPL (SD = 9.9 dB) was reached, comparable with the *standard* condition.

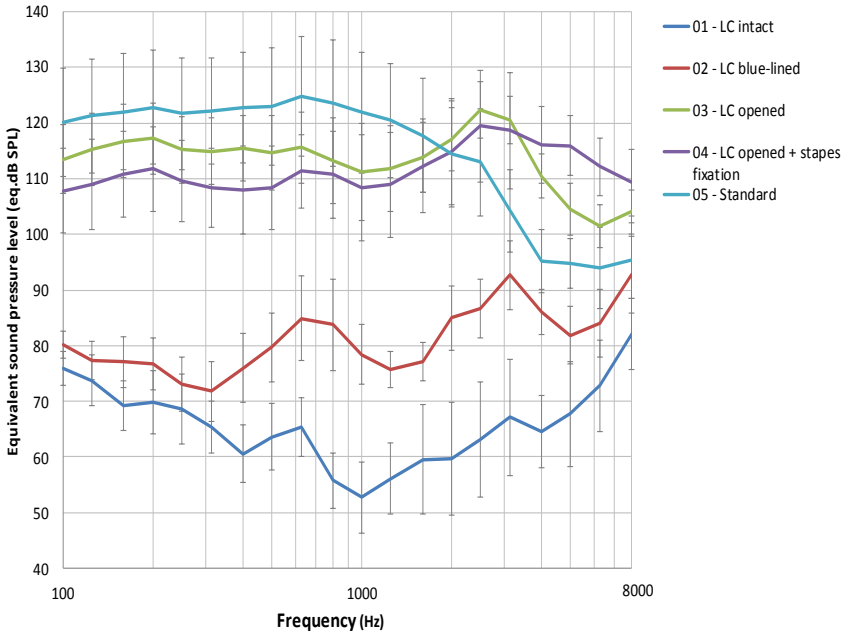


Figure 5.5 Mean (n=5) equivalent sound pressure level output (L_E) in response to DACI stimulation in different coupling positions with error bars as standard errors.

In case of stapes fixation, DACI stimulation at the opened LC resulted in a peak of 124.5 eq. dB SPL (SD = 15.3 dB). As with *LC opened* stimulation, *LC opened with stapes fixation* also resulted in a shift in resonance frequency and improved performance in a wider frequency range at the minor expense of low-frequency amplitude, compared to the *standard* condition. Means, standard deviations and peak values in 3 adjacent frequency ranges for the 5 different conditions are detailed in Table 5.2.

Calculated L_E data were normally distributed for all conditions and all frequency ranges. Paired samples t-test showed similar results to RW velocity analyses, except in one case. In contrast to RW velocity, which showed a difference between the *LC intact* and *LC blue-lined* conditions in the high frequency, L_E analyses revealed added value of the *LC blue-lined* condition over the *LC intact* condition for the low ($t(4)= -3.56$, $p= .024$, $r= .87$) and high ($t(4)= -2.95$, $p= .042$, $r= .82$) frequency range. The same trend was observed for the middle frequency range, but it was not statistically significant ($t(4)= -2.47$, $p= .069$, $r= .78$).

Table 5.2 Mean (n=5), peak and standard deviation (SD) of equivalent sound pressure level for the 3 frequency ranges and 5 conditions (in eq. dB SPL).

Condition	Low		Middle		High		$L_{E,max}$	
	Mean	SD	Mean	SD	Mean	SD		SD
LC intact	72.4	8.1	61.3	21.4	76.8	15.3	95.8	17.9
LC blue-lined	83.9	10.9	85.3	8.6	95.1	11.9	105.4	11.3
LC opened	115.9	14.4	119.2	13.0	115.2	9.2	126.2	9.9
LC opened + stapes fixation	110.5	16.1	115.9	21.0	119.9	13.8	124.5	15.3
Standard	123.1	22.9	119.8	22.8	102.8	12.2	126.8	20.5

5.5 Discussion

5.5.1 Experiments

Although the ASTM standard describes a method on temporal bone preparations (Rosowski et al, 2007; ASTM, 2005), whole heads were used in this experimental study, representative of real-life DACI implantation. Using a complete head avoids the possible exclusion of physiological third-windows (paths for leakage flow). In the low frequencies, the included heads (except for head 6) showed ossicular chain mobility marginally within the criterion of the 95% CI range of Rosowski's group. This is consistent with the wide variability described before in living humans with normal hearing (Whittemore et al, 2004). Since the focus of the investigation was on different coupling conditions within each head, minor variability between heads was acceptable. In addition, by calculating the L_E relative to the individual middle ear transfer function, intrinsic variability of each head was taken into consideration. As in the study by Chatzimichalis et al. (2012), evaluation of DACI performance was derived from measured RW velocity. Maier et al. (2013) already remarked that use of RWM displacement as an output measure for some input forces requires some degree of assumption. Coupling an actuator to the LC, at the side of the scala vestibuli, creates a kind of forward stimulation with the RWM acting as a pressure outlet (Stieger et al, 2013). Nevertheless, underestimation of equivalent sound pressure output is possible to some extent. As discussed further, input

impedance of the cochlea does not appear to be changed by DACI application in the *LC opened* condition (though covered with fibrous tissue).

Taking into account verification by induced stapes footplate fixation performed in all heads, mean attenuation was measured via acoustic stimulation with an undisrupted ossicular chain in 4 and 3 heads for stapes and RW velocity, respectively. A reduction in stapes velocity of at least 30 dB has previously been described (Nakajima et al, 2005), and 20 dB for RW velocity, which is more than the respective 12 dB and 15 dB reduction in stapes and RW velocity reported in our study. One reason for the difference might be that fresh-frozen heads are less opted for drying of the dental acrylic; another reason is the creation of a third-window. In the *LC opened* condition, a canalotomy was performed, thereby creating a third-window on the side of the scala vestibuli, possibly represented by conductive hearing loss in vivo (Merchant & Rosowski, 2008). Although this site was covered with fascia and the artificial incus, a certain degree of energy loss can occur during fluid displacement. The third-window leads to an alternative pressure outlet instead of the pressure difference between the oval and round window (Wever et al, 1949), so the impact of stapes fixation can be minimized. Feasibility measurement with acoustic stimulation in case of stapes fixation was performed in one head, indicating that RW velocity is significantly different if the opened LC is covered or not with fascia and the actuator ($p < 0.001$). Further studies are required to investigate the effect of LC canalotomy on the magnitude and phase of the middle ear transfer function, and on cochlear micromechanics. Use of intracochlear pressure sensors, regardless of experimental alterations such as stapes fixation or stapedectomy, may help to shed light on in this matter (Olson, 1998; Nakajima et al, 2009).

5.5.2 LC stimulation

Experimental DACI stimulation at the level of the lateral canal was investigated in different conditions. The inertial mode for bone conduction hearing is the strongest in the lateral direction when the axis of the vibration coincides with the axis of the position of the cochlea (Tonndorf, 1966). Subsequently, the first two conditions (*LC intact and LC blue-lined*) aimed to evaluate DACI performance without opening the canal, thereby avoiding limited risks like mild

hearing loss (9%), instability or even vertigo, as described for semicircular canal plugging procedures (Chen et al, 2010; Ramakrishna et al, 2012). Output measured at the RW was, however, insufficient for amplification in either of these two conditions. L_E analyses, on the other hand, revealed modest but significant added value of the *LC blue-lined* condition over the *LC intact* condition for the low (p= .024) and high (p= .042) frequency range. Once the LC was opened, large-spectrum mean output of 116, 119 and 115 eq. dB SPL in the lower, middle and higher frequency range, respectively, and a peak output of 126 eq. dB SPL were obtained. This performance is fully consistent with previous temporal bone investigations, such as the study by Maier et al. (2013) using 1 V RMS input to an actuator coupled to the RW. With the DACS-PI (Phonak Acoustic Implants SA, Switzerland) coupled to the oval window at an input of 0.3 V RMS, an $L_{E,max}$ of 110 eq. dB SPL was recorded (Chatzimichalis et al, 2012), but higher input voltages were not investigated in this study. As the system acts linear, going from 0.3 V to 1 V RMS would mean an increase of 6 dB SPL. Interestingly, in the current study, no sharp resonance peak was noted in RW velocity with DACI stimulation of the LC, in contrast to *standard* oval window coupling (Bernhard et al, 2011). In standard oval window coupling with stapes prosthesis, this resonance peak is damped after the healing process in vivo. In addition to increased performance in a wide frequency range, the LC stimulation pathway could potentially facilitate fitting issues, circumventing the need for damping the peak to avoid overstimulation.

No loss of DACI performance, stimulating the LC, was observed when the stapes footplate was fixed, as revealed by pairwise comparisons (p= .168). Regarding RW velocity measurement, stapes fixation resulted in higher values in the high frequency range than in the LC opened alone condition (p= .033), although this was not confirmed by L_E comparisons. This is in line with findings on third-window stimulation with AMEIs (Lupo et al., 2012) in case of stapes footplate fixation. Accordingly, it may be hypothesized that stimulation of a third-window, in the context of stapes fixation, with an unobstructed round window, results in improved impedance at the base of the cochlea. Achieving similar peak output to the LC opened condition, the DACI device can be applied in case of stapes footplate fixations, such as otosclerosis. It should be noted that phase investigations were not taken into account and warrant further study.

Unlike conventional DACI coupling after calibrated-hole stapedotomy a stapedectomy was performed in the current study, as a laser was not available in the temporal bone laboratory. The absence of a stapes footplate resulted in lower than expected high-frequency amplification, although the results were consistent with RW DACI stimulation and DACI stimulation with a 0.8-mm stapes piston (Maier et al, 2013; Chatzimichalis et al, 2012). Neither *LC opened* condition, with or without stapes fixation, showed any significant difference compared to the *standard* condition, demonstrating that in terms of performance, LC stimulation after canalotomy with fascia interposition could be an alternative for the *standard* DACI procedure. Compared to an AMEI device coupled to the RW (Pennings et al, 2010), much higher velocity values, i.e. peak values up to -56 dB m/s versus about -90 dB m/s, were obtained with DACI stimulation in both *LC opened* and *standard* conditions, confirming the powerful output of the investigated implant.

5.5.3 Clinical implications and future research

Coupling a powerful acoustic hearing implant to an anatomically easy accessible site can have far-reaching clinical implications. As mentioned before, in a number of disorders, such as chronic otitis media with tympanosclerosis, radical cavities, congenital malformations or advanced otosclerosis, neither the oval window nor RW may be available for adequate coupling (Lupo et al, 2012). Moreover, if facial nerve exposure and time-consuming surgical actions like stapes prosthesis coupling to the actuator are excluded, surgical risks associated with the DACI procedure can be minimized (Verhaert et al, 2013a).

The described LC stimulation technique derives from closed fenestration procedures introduced at the beginning of the 20th century by Jenkins and Holmgren, and later refined by Sourdille and then by Lempert (1952). Vertigo, instability and induced hearing loss are fairly limited in experienced hands. In contrast to open fenestration surgery, contact with open air, epidermal growth and granulation tissue is avoided, minimizing risks of vertigo or dizziness, similar to plugging procedures. Furthermore, the size of the canalotomy in our study was only 0.7 mm, and it was covered with fascia. Future research will clearly need to investigate long-term biology of the canalotomy, assessing, for example, risks of bony tissue regrowth in case of non-stimulation and effects on

the vestibular system in the event of non-linearity. It is known that bone conduction implants do not affect the vestibular organ. It can therefore be assumed that acoustic stimulation, with frequencies above 100 Hz, is well above vestibular stimulation frequency range. A shortcoming in this cadaver study is that possible non-linear effects causing vertigo cannot be investigated. LC fibrosis could potentially hinder the recorded output. Electrophysiological measurements, first in animal models as demonstrated in AMEIs in case of third-window stimulation (Lupo et al, 2012), then in humans using reliable techniques, can provide objective feedback on adequate coupling to the inner ear, and also on the correct auditory processing in the cochlea and brainstem (Verhaert et al, 2014a).

Finally, with the development of specially designed drills or robot-controlled microdrill that avoid perforation of the membranous labyrinth, results can be reproducible and risks well controlled (Coulson et al, 2013). Also, laser-assisted calibrated hole techniques can be used for the canalotomy.

5.6 Conclusions

This study demonstrates the feasibility of LC stimulation with a DACI device for severe to profound hearing loss. The surgical techniques of coupling the device to the LC with fascia interposition are described. Opening the lateral semicircular canal resulted in performance efficiency similar to conventional oval window coupling. Stapes fixation did not impede DACI performance at the level of the LC. Future studies need to address the long-term effects of LC stimulation and its impact on cochlear micromechanics.

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Chapter 6
General discussion and conclusions

An idea, like a ghost, must be spoken to a little before it will explain itself. - C.Dickens.

6.1 Summary of research findings

The general objective of this PhD project was the investigation and development of objective measures and a new coupling strategy for direct acoustic cochlear stimulation, in addition to the clinical application and audiological evaluation of DACI in subjects with severe to profound MHL.
The core findings of this PhD project are:

- Systematic review of the current literature revealed that AHIs are effective in terms of speech understanding in quiet, patient-reported outcome measures and safety regarding residual hearing for the treatment of mixed hearing loss. Although already investigated for passive percutaneous BCIs to a certain extent, for other acoustic hearing implants more comprehensive data are needed on coupling strategies to the inner ear and the comparison with best-fitted alternatives, certainly with respect to speech understanding in noise (Chapter 2).
- Direct acoustic cochlear stimulation provides a significant improvement of the speech perception in quiet and in noise compared to the preoperative aided condition. It improves significantly the ability of patients to communicate in everyday situations and their quality of life (Chapter 3).
- DACI treatment can be considered a safe and effective hearing treatment (Chapter 3).

- ABRs and ASSRs can be recorded in subjects with a DACI. Electrophysiological thresholds can be determined through the combined information of the amplitude response growth function and the phase delays of the responses, using a statistical method (Chapter 4).
- AEPs latencies were in agreement with electrophysiological auditory pathway studies (Chapter 4).
- DACI stimulation at the level of the lateral semicircular canal (LC), investigated in human cadaver heads, can facilitate the surgical implantation. Stimulation at an opened LC resulted in an output similar to the oval window coupling, confirming its efficiency (Chapter 5).
- Induced stapes footplate fixation did not impede the DACI output when stimulating the opened LC (Chapter 5).

In the following sections, both clinical as well as experimental topics will be discussed separately including remarks or shortcomings, reflections and future perspectives.

6.2 Severe to profound MHL treatment revisited

Before the introduction of DACIs, the treatment of severe to profound MHL mainly consisted of a hearing aid, whether or not in combination with a middle ear procedure; in more severe cases a CI was inserted. Other AMEI could not provide sufficient output (see Chapter 2). With correct preoperative selection of subjects, the DACI treatment can offer an important improvement of speech in noise understanding with a relatively short (less than three months) rehabilitation period, as shown in Chapter 3. In the current PhD project, the device was still under investigational use and implemented in a selected group of centers of excellence in hearing implants. From a clinical perspective, several issues can be discussed.

Clinical indication Especially for advanced otosclerosis, the DACI treatment can be added to the ongoing debate between preservation of the remaining cochlear function versus a cochlear implantation with electrical stimulation. The main point of discussion is the presence of variable results in case of stapedotomy alone with HA in comparison to CI (Merkus et al, 2011;

Sheehy, 1978). Despite the fact that CI is associated with a higher chance of acceptable speech understanding in quiet, the possibility of retaining acoustic hearing, cues for enjoying music and a shorter rehabilitation period persuade most ENT-specialists to perform a stapedotomy prior to cochlear implantation. In certain studies, a fairly high (38%) risk of facial nerve stimulation has been reported for these patients (Rotteveel et al, 2004). On the other hand, some reports show a clear improvement in open-set speech understanding in quiet with stapedotomy plus HA in more than half of the advanced otosclerosis cases (Lachance et al, 2012). In that study, however, only 16 subjects were studied, some bilateral. Also, the intensity of the open-set speech understanding testing was not defined and no speech in noise scores were provided. As reported in Chapter 3, speech in noise understanding results, obtained with DACI treatment, with a mean SRT score of + 2.6 dB SNR, are very encouraging. These results, however, cannot be extrapolated for comparison with cited CI scores, ranging from + 2 to + 16 dB SNR (van Wieringen & Wouters, 2001) because of a wide range of profoundly deaf subjects. Important for real-life communication, as suggested in Chapter 1, 2 and 3, the improvement of speech in noise understanding is very encouraging for such patients. AMEI and BCIs, even the most powerful BAHA, cannot overcome 50 dB HL inner ear hearing loss. The powerful, large spectrum amplification provided by a DACI surpasses not only preoperative best-aided therapy but also alternatives such as a stapedectomy plus HA or BCI. As otosclerosis or other causes of MHL equally affects the lower frequency hearing, inserting a shorter CI electrode in the cochlea, like in electro-acoustic stimulation for the preservation of low frequency hearing, would seem less adequate. Also it should be noted that an electrode insertion with too flexible electrode arrays can be difficult in case of cochlear otosclerosis (Toung et al, 2004).

So far, all subjects descripted in Chapter 3, except for the one subject with additional hearing loss, are wearing their speech processor. Results, also from a previous study (Lenarz et al, 2013), indicate stable scores up until now. Obviously, longer follow-up period than two to three years is needed to observe long-term evolutions. Certainly for slowly progressive advanced otosclerosis cases, aided hearing will preserve and enhance spiral ganglion neuron survival, important for better CI performance later on (Blamey et al, 2013). Cochlear

implantation remains feasible after DACI implantation but cost-effectiveness studies are needed to investigate this sequential treatment. With a more rapid rehabilitation, less than 3 months as can be understood from Chapter 3, the DACI treatment seems advantageous over electrical cochlear implantation, especially for certain older patients with less means of training or with mobility issues. This hypothesis, however, needs further comparative study. In very advanced otosclerosis cases though, with important cochlear reorganization, a window of opportunity for CI should be taken into account (Merkus et al, 2011), as mentioned before. Future research, for this clinical perspective, should include prospective comparisons between stapedotomy plus HA versus DACI versus CI.

DACI fitting PROM indicate a relatively high aversiveness score at three months post-activation in Chapter 3, also in comparison to previous reports (Lenarz et al, 2013). Aversiveness is related to negative reactions to environmental sounds. This score can partially be explained by the relatively short measurement point of three months and by necessary improvements to be made in the current fitting procedure. The current first fitting session relies on the intra-operatively measured transfer function of the implant and on the most comfortable loudness level. Because of the healing process, however, in some subjects the implant's transfer function can be altered possibly resulting in suboptimal coupling efficiency and unexpected performance results initially. Evaluating and adjusting the current fitting rule to real ear measurements, similar to the NAL fitting rule, with higher maximum performance possibilities and more adequate amplification at the lower intensity of 50 dB SPL, could maybe improve patient-reported outcome scores. While also profound hearing loss subjects are being implanted, the compensation for certain non-functional cochlear regions, known as dead regions, should be taken into account when developing new fitting algorithms. Recently, the prevalence of dead regions was investigated in new and existing hearing aid users, showing a common (1 out of 3) but mostly clinically irrelevant presence of a dead region (Pepler et al, 2014). Only in 3% of the users, an extensive dead region was present. New insights in the pathophysiology of hearing loss, as mentioned in Chapter 1, are to be taken into consideration when developing new speech processing algorithms for acoustic hearing implants, just as in hearing aids and CIs (Pfingst et al, 2004). As

with all newly introduced therapies, a learning curve for surgery and fitting, together with an increasing experience from the implanted subjects, is within normal expectancy. The stability of the results, probably due to the fixation system, is very encouraging. With a very recently updated speech processor and gaining clinical experience, scores could equally improve. A longer follow-up multicenter study, focusing on the optimization of the fitting parameters, is planned for the subjects implanted so far.

Predictive factors Retrospective analysis of the gathered aspects on radiological, audiological and surgical data of 23 subjects from 4 centers (Leuven, Antwerp, Hannover, and Nijmegen) is planned in the forthcoming months. It is hypothesized that the duration of preoperative HA-use influences the audiological outcome of the DACI-user. Very little variability in the surgical parameters (width of stapedotomy, type of stapes piston etc.) is being observed. One of the few subjects with poor improvement identified in Chapter 3, despite of uncomplicated DACI surgery and postoperative healing, has been diagnosed with auditory neuropathy, explaining his poor outcome. Subsequently, tools will have to be evaluated to sharpen the indication range and to predict outcome, as this has been done for CI as well in the past. Neural degeneration could influence the final speech performance, as in cochlear implantation.

Two ears Stereophony, considering both ears, has not been taken into account sufficiently in this project. Stereophony is regarded as a prerequisite for appropriate directional hearing and binaural hearing. In Chapter 3, only subjects with contralateral moderate to profound hearing loss were included. Known as the Belfast rule of thumb, interaural hearing differences play an important role for the degree of success reported by the patients themselves after ear surgery (Smyth & Patterson, 1985; Hazenberg et al, 2013). Another perspective is the analysis of the binaural cues with the DACI device. Although not reported, spatial hearing questionnaires have been administered before and after DACI surgery in our single center. Bilateral fitting with a HA or another AMEI has been performed in the clinical setting, but data gathering is still ongoing presently. Future research on DACI will need to include localization tasks, investigating the preservation of fine structure and interaural cues, and exploring other possible advantages over cochlear implantation. If

reimbursement will be provided, the number of implanted subjects will grow and clinical experience will grow rapidly.

6.3 AEPs for DACI

As described in Chapter 4, for the first time ABRs and ASSRs have been recorded through a digital acoustic hearing implant in humans. With the acoustic stimulation setup, stimulation artifacts made it impossible to analyze responses. With the direct stimulation setup, using click trains, stimulation artifacts could be removed completely, and responses could be successfully recorded in all subjects. At this stage, sinusoidally amplitude-modulated stimuli, being more frequency-specific, could not yet be used. They provoke unpredictable artifacts on the experimental bench setup and therefore they were not applicable in vivo. Other more frequency-specific stimuli, such as tone burst or chirps (Kristensen & Elberling, 2012), do not provoke unpredictable artifacts with direct stimulation when tested on the experimental bench setup. In recent studies about auditory threshold determination in adults at a high rate of stimulation, chirp stimuli are associated with shorter detection time than a click (Elberling et al, 2007). Further methodological study, also with chirps, is needed with direct stimulation, similar to electric ASSRs in CI (Hofmann & Wouters, 2010).

Electrophysiological thresholds, and their relation to behavioral thresholds, have been determined in this study. Mean differences between behavioral and electrophysiological thresholds were 12, 19 and 26 dB for electrophysiological thresholds based on 40 and 90 Hz ASSRs and ABR peak V, respectively. As a next step, correlations between electrophysiological and behavioral thresholds should be investigated in a larger study cohort. The reported mean differences for ASSRs concur with values reported for acoustic stimulation, indicating an overall Pearson correlation up to 0.83 (Alaerts et al, 2010). Even if only investigated in a small group of DACI-wearers, potential AEP implementations can be developed in the near future. Automatic fitting applications will need reliable detection of ASSRs, similar to the challenges of ASSR detection for automatic CI fitting in children as suggested before (Hofmann & Wouters, 2012). But it can be interesting to facilitate the initial postoperative fitting session. The device is currently not indicated for children. Future research

should therefore mostly focus on recording intra-operative feedback of direct cochlear acoustical stimulation, reducing the recording time, and the post-operative determination of preliminary fitting parameters.

Another perspective is the development of an electrophysiological alternative for current intra-operative measurements. These measurements analyze the coupling and performance of the device through velocity measurements done with an LDV setup. Other applications, such as middle ear admittance measurements, are currently being tested but lack information on the auditory system coupling. More frequency-specific stimuli for ASSR recording, such as tone bursts or chirps, should be developed to obtain the transfer function of the actuator. Using a frequency sweep technique, or by sweeping through different values of a stimulus parameter, as demonstrated for visual stimuli by Regan (1973), can have interesting applications for recording steady-state responses (Picton et al, 2003). If the general shape of the resulting graph is known beforehand, the averaged graph can be smoothed to fit this shape. Then the sweep technique can be more rapidly recorded and more efficiently than multiple individual measurements. Theoretically, the ideal output graph is known for each produced DACI implant, for this reason the sweep technique can be applied, estimating the correct coupling to the inner ear. Another valuable intra-operative application could be ECoG with a direct stimulation setup focusing just on the DACI coupling to the cochlea.

With the indication criteria extending to profound MHL, the development of the proposed techniques might also provide an objective measure for the correct auditory processing in the cochlea and brainstem for difficult differential diagnosis cases. Absent electrophysiological responses during intra-operative measurements may be related to insufficient cochlear reserve and pose an indication to convert the surgery to a cochlear implantation. As remarked before, AEPs have the advantage that they can be recorded both intra- as postoperatively and provide information beyond merely the coupling to the cochlea, as do ECoG.

6.4 Lateral canal stimulation

An important challenge of the DACI treatment is the surgery involved. Although stapes surgery is commonly performed, the implantation is overall not an easy

procedure. It requires a high level of surgical expertise. In Chapter 5, the stimulation of the inner ear through an alternative pathway has been investigated experimentally. As a first step, the performance of the device when coupled to the LC has been documented by measuring the output at the level of the round window. If a reliable stimulation can be developed in this way, then it might reshape the landscape of DACI, and possibly AMEI, implantation. The first parts of DACI surgery would become easier, as a standard mastoidectomy would suffice. Opening the facial recess would become unnecessary, avoiding rare risks of facial paralyses due to drilling injuries, exposure or impression on the facial nerve (House & Luxford, 1993). In some cases, neither the oval nor the round window can be exposed, directing the surgeon to perform a 'third-window' (Pau & Just, 2010). For all the above reasons, the LC stimulation has been investigated. Regarding inner ear damage, the proposed surgical technique in Chapter 5 can be considered as a safe procedure, similar to posterior canal plugging or stapedotomy procedures (Chen et al, 2010; Parnes et al, 2003). The reported performance, with a peak performance up to 126 eq. dB SPL with LC opened and 125 eq. dB SPL in case of stapes fixation, respectively, is well within range for the treatment of severe to profound mixed hearing loss. Similar output was achieved in another experiment with RW stimulation with a DACS-PI actuator (Maier et al, 2013). Both LC and RW stimulation with a DACI achieve higher outputs than experiments that described 'third-window' coupling with an AMEI (Lupo et al, 2012). However, comparisons should be interpreted with care due to different stimulation pathways and thus different cochlear input impedance.

A shortcoming of this feasibility study is the lack of in vivo experiments. Fenestration surgery, as described by Sourdille and later developed endaurally by Lempert in the first half of the 20th century (Shambaugh & Wiet, 1979), was associated with frequent reclosing of the canalotomy. Recurrently, spontaneous sealing was induced by granulation due to contact with the external air and the radical cavity. This could possibly be avoided with the surgical technique described in Chapter 5 where contact neither with epidermal tissue nor with external air is present. From posterior canal plugging procedures, it could be expected that fibrosis in the lumen of the canal occurs at the level of the canalotomy. Covering it with fascia can even induce fibrosis. To that end the

analysis of short- and long-term biology of this canalotomy in response to continuous DACI stimulation remains to be performed in vivo. Its analysis can have implications on the DACI outcome reported in this project at long-term. Once confirmed in animal studies, the coupling of the DACI to the LC can be monitored with electrophysiological methods in humans (as described in Chapter 4).

Another point of future research is the possible impact on vestibular function. In Chapter 4 and in Bernhard et al (2011), it has been shown that the DACI system provides linear amplification up until high amplitudes and that non-linear distortion is almost absent. Possible fibrosis at the LC coupling site, however, can induce non-linear spreading of acoustic energy, causing vestibular symptoms. Experimental study on chinchillas, useful also for electrophysiological testing (Lupo et al, 2012), could help elucidating this research question.

Finally, as mentioned in Chapter 5, the impact of creating and stimulating a 'third-window' at the scala vestibule side of the cochlea, albeit covered with fascia and the actuator's tip, should be investigated in terms of cochlear mechanisms. Whereas the role of 'third-window' has been investigated before (Merchant & Rosowski, 2008), our research is the first to report the DACI stimulation at this site. Moreover, the impact of a canalotomy on the cochlear impedance in case of stapes footplate fixation has not been investigated before. For this research question, intra-cochlear pressure sensors may help to shed light on this matter (Nakajima et al, 2009; Olson, 1998).

Appendix

A.1 MEDLINE search strategy (Chapter 2)

#26 (#15 AND #25)	1482
#25 (#17 OR #19 OR #21 OR #23 OR #24)	14662
#24 prosthes* AND (middle ear)	2231
#23 (implant OR implants) AND (middle ear)	2314
#21 “Cochlear Implants”[Mesh] OR (cochlear implant*)	9628
#19 “Bone Conduction”[Mesh] OR BAHA OR (bone conduction implant)	3019
#17 “Ossicular Prosthesis”[Mesh] OR “Ossicular Replacement”[Mesh]	1036
#15 (#5 OR #7 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)	12885
#14 (#5 AND (middle ear malformation))	71
#13 tympanosclerosis	409
#12 (#5 AND (ear abnormalities))	157
#11 otoscleros*	5213
#10 (Otitis Media) AND chronic*	6681
#9 (“Otitis Media”[Mesh]) AND chronic*	5410
#7 “Otosclerosis”[Mesh]	4633
#5 (#2 OR #3 OR #4)	1087
#4 (hearing loss) AND mixed	1087
#3 (mixed hearing loss)	1007
#2 “Hearing Loss, Mixed Conductive-Sensorineural”[Mesh]	165

A.2 Study selection (Chapter 2)

Participants: Patients > 18 yrs with a mixed hearing loss

Interventions: Active middle ear implants OR osseointegrated bone-conduction implant (BCI) OR cochlear implants OR stapedotomy OR ossicular prosthesis OR DACS OR conventional hearing aid

Comparator: HA (if stated), BCI, none

Outcomes: Hearing: pure tone audiogram (PTA)
Speech in quiet, speech in noise
Safety (complication rate)
PROM (patient-reported outcome measures): validated questionnaires

Study design: Randomized controlled trials, cohort studies, case-control trials (also when subjects act as their own controls)

A.3 Eligibility criteria DACI study (Chapter 3)

Inclusion criteria

- Eighteen years of age or older
- In the ear to be implanted:
    - Severe to profound mixed hearing loss
    - Conductive hearing loss due to otosclerosis, failed stapes surgery or other middle ear and/or external ear pathologies and/or anomalies
    - Well ventilated middle ear
    - Closed eardrum with normal anatomical position except for outer ear canal anomalies
    - Bone conduction thresholds are equal to or worse than 40 dB HL and equal to or better than 80 dB HL in the frequencies 0.5 kHz, 1 kHz, 2 kHz, 3 kHz and 4 kHz
    - Air-bone-gap is equal to or greater than 20 dB on at least 3 out of the 5 frequencies 0.5 kHz, 1 kHz, 2 kHz, 3 kHz and 4 kHz
- In the contralateral ear:
    - Moderate to profound hearing loss

Exclusion criteria

- Active chronic otitis media, in the ear to be implanted
- Contraindication for opening of the inner ear, in the ear to be implanted
- Unwillingness or inability of the subject to comply with all study requirements
- Unrealistic expectations on the part of the subject regarding the possible benefits, risks and limitations that are inherent to the procedure and the device
- Medical conditions that would contraindicate undergoing surgery or participation in this study
- Sudden hearing loss
- Insufficient mastoid and/or ear canal size or too large mastoid cavity (to be checked on CT scan)
- MRI required for any disease follow-up
- Best aided speech perception in quiet at 65 dB is 75% or more in the ear to be implanted

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Curriculum vitae

Nicolas Verhaert was born in Lier, Belgium, on 25 March 1979. He received secondary education (Latin-Mathematics) at the Onze-Lieve-Vrouwecollege Antwerp and graduated in 1997. After completing Bachelor studies at the Facultés universitaires Notre-Dame de la Paix in Namur, he started a Master in Medicine in Leuven. During his studies, he spent four months for medicine training at the University Hospital in Santiago (Chile). In 2004, he obtained a Master's degree in Medicine with greatest distinction from the University of Leuven. From 2004 to 2009, he was engaged as a trainee in Otorhinolaryngology, Head and Neck Surgery; starting with three years at the University Hospitals Leuven, followed by two years at the General Hospital of St Jan Bruges, Belgium. In August 2009, he completed his training, graduated at the University of Leuven and was recognized by the Belgian ministry of Health as Specialist in Otorhinolaryngology, Head and Neck surgery. After his graduation, he spent six months at the University Hospitals of Lyon (France) and one year at the Hannover Medical School (Germany) for otology and neuro-otology fellowships. From August 2011, he has been a staff member at the Department of Otorhinolaryngology, Head and Neck Surgery of University Hospitals Leuven and a member of the research group ExpORL at the Department of Neurosciences of KU Leuven, the latter under the supervision of Prof. Jan Wouters. He received a clinical PhD Fellowship Grant from the Research Foundation Flanders (Oct 2011-Sep 2013) and from the Research Council of the University Hospitals Leuven (Oct 2013-Oct 2015). His research interests are in the domain of otology and audiology in general, and more specifically in auditory evoked potentials, hearing implants and temporal bone study.